

A THESIS

ENTITLED

CARDIORESPIRATORY AND METABOLIC
STUDIES IN SHOCK AND CRITICAL
ILLNESS

BY

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Summary

REFERENCES

Dedication

This work is dedicated to my family and patients: past,
present and future.

Declaration

I declare that all of the work described herein was carried out by myself, in the Intensive Therapy Unit, Western General Hospital, Edinburgh and the Department of Medicine, Royal Infirmary, Edinburgh between 1989 and 1992. Some of the work was done in collaboration with colleagues, as detailed below. The data analysed in Chapter 3 includes that of 20 patients studied in the Intensive Care Unit, University Hospital of South Manchester, Manchester.

Chapter 2 - Dr IS Grant, Dr IR Armstrong.

Chapter 3 - Dr SJ Mackenzie, Dr P Nightingale,
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ABSTRACT OF THESIS

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Name of Candidate Graham Robert Nimmo
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Haemodynamic monitoring and measurement of acid-base status are routine in the assessment and management of the critically ill. It is known that tissue hypoxia results in anaerobic metabolism, hyperlactataemia and lactic acidosis. The role of the cardio-respiratory system in providing adequate oxygen to respiring tissues is fundamental in physiology. Acute derangements of oxygen transport result in a spectrum of disease from minor illness to life threatening conditions such as shock and multiple organ failure. Despite this, it is only relatively recently that attempts have been made to monitor and study systemic oxygen delivery (DO_2) and oxygen consumption (VO_2) in the Intensive Care Unit. Studies of the sequential, concurrent changes of cardio-respiratory and metabolic parameters, particularly in relation to resuscitation, organ failure support or sedation have been lacking.

Methods are described for measurement of systemic haemodynamics, DO_2 , VO_2 , arterial blood lactate and pyruvate concentrations, urinary kallikrein and plasma renin activity (PRA).

In patients undergoing resuscitation from shock three groups were defined on the basis of the responses of arterial blood lactate (ABL) concentrations. The first group had hyperlactataemia which corrected following therapy which achieved significant increases in mean arterial blood pressure (MAP: $p < 0.01$) and DO_2 ($p < 0.005$).

Group two had similar lactate levels, but vigorous therapy, which increased MAP significantly ($p < 0.05$) did not increase DO_2 . ABL concentrations remained elevated, and mortality was high. These differences emphasise the importance of simultaneous reversal of hypotension and attainment of adequate DO_2 . In the third group, despite severe cardio-respiratory abnormalities hyperlactataemia was not seen. Shock may occur with normal ABL concentrations. In patients with shock and adult respiratory distress syndrome (ARDS) an elevated ABL has been proposed as a marker of delivery dependent VO_2 , a potential indicator of tissue hypoxia. Septic shock and ARDS patients were classified on the basis of normal or elevated ABL concentrations. The level of ABL had no value in predicting the response of VO_2 to changing DO_2 in either the grouped data, or in individual patients. The absence of hyperlactataemia in ARDS does not preclude the presence of delivery dependent VO_2 , and by implication tissue hypoxia.

The anaesthetic induction agent propofol has been used for sedation in adult critically ill patients. In a group of ventilated, invasively monitored patients its effects on cardiorespiratory function were documented. Heart rate and MAP fell significantly ($p < 0.05$) but DO_2 and VO_2 were unchanged despite a significant increase in the sedation score ($p < 0.01$), suggesting there was no improvement in overall oxygen supply/demand balance.

Theoretical objections exist to the use of lactate-containing haemofiltration (HF) fluids in shock with acute renal failure. Blood lactate rose during HF ($p < 0.001$), with haemodynamic stability and no deterioration of acid-base status. In an ovine model of septic shock treatment with the protease inhibitor aprotinin had beneficial effects on MAP, creatinine clearance and PRA. Kallikrein activation may be important in the pathophysiology of septic shock, and afford a specific target for therapy.

CHAPTER 1

RATIONAL FOR THE STUDIES AND REVIEW OF THE LITERATURE

1.1. Cardiorespiratory and acid-base physiology

1.1.1. Introduction

The maintenance of life is critically dependent on the provision of adequate oxygen to the respiring cells of the body (Barcroft 1920, Flenley 1978, Abraham 1986). The adequacy of this supply depends on the balance between oxygen requirements and the volume of oxygen delivered to the tissues. The supply of oxygen depends on the complex interactions of the elements comprising the highly developed cardio-respiratory system, which allows the transfer of atmospheric oxygen from alveoli to mitochondria (Miller 1982). The individual parts of this system are the lungs, heart and circulation. Although in clinical practice these elements are often regarded individually, they are functionally indivisible. The dynamic physiological components of the cardio-respiratory system are: cardiac output, haemoglobin concentration, the percentage of haemoglobin saturated with oxygen in arterial blood, dissolved oxygen in arterial blood, the affinity of haemoglobin for oxygen and the distribution of perfusion (which relies on systemic blood pressure and the local balance of vasoconstriction and vasodilatation). All but the last of these can now be measured routinely at the

bedside in critically ill patients.

The achievement of normal metabolism relies on the ability of this system to deliver oxygen to the appropriate sites, and in sufficient quantities to meet demand. In clinical practice we can measure whole body oxygen transport (Edwards 1990) but still rely on remote and global markers such as blood lactate concentration to assess the overall supply/demand relationship. The dynamic relationship of blood lactate concentrations and oxygen transport variables during resuscitation have only recently been considered.

The fundamental importance of deficiencies in all components of this system in critically ill patients have been emphasised by Nightingale (Nightingale 1990) and Lister (Lister 1991), but several crucial, practical points are highlighted here.

- 1) It has been repeatedly demonstrated that clinical assessment, even by experienced clinicians, is often inaccurate in the acutely ill (Connors 1983, Eisenberg 1984).
- 2) The ability of patients to maintain blood pressure by vasoconstriction, to the detriment of flow and perfusion, has been documented in Adult Respiratory Distress Syndrome (ARDS), cardiogenic shock and multiple trauma (Clarke 1991, Creamer 1990, Brown 1992, Edwards 1988). Conversely, in sepsis, hypotension may be associated with a hyperdynamic circulation, but severe regional blood flow maldistribution causes critical

tissue hypoxia, despite the high cardiac output (Maclean 1967, Duff 1969).

3) Measurement of urine output and documentation of 'vital signs' poorly reflect the adequacy of resuscitation (Dries 1991).

Evidence is accumulating that survival rates can be improved in sepsis, trauma, high-risk surgical patients and low flow states if therapy is directed at improving overall oxygen transport (Tuchschmidt 1992, Edwards 1991, Shoemaker 1988, Boyd 1993, Sumimoto 1991). This evidence, coupled with the need to employ treatments with a potential for worsening of the overall and regional oxygen supply/demand balance such as catecholamines and positive end-expiratory pressure (PEEP), necessitate a low threshold for invasive monitoring and oxygen transport measurement in the severely ill, as advocated by the European Society of Intensive Care Medicine (Bennett 1991 i). This has major implications for the practice of, and the provisions for, intensive care in the United Kingdom.

1.1.2. Tissue hypoxia

The basic nature of the circulation, cardiac function and blood flow have been understood since Harvey's original treatise (Harvey 1628). Priestley's discovery of oxygen (dephlogisticated gas) in 1794 led rapidly to its use in clinical practice by Beddoes and Watt (Beddoes 1794). Despite these initial discoveries, it

was not until early this century that the connections between hypoxia, circulatory compromise and lactic acidosis were first suggested (Macleod 1921). In 1920, Barcroft stated that research into the supply of oxygen to the tissues was "urgent, as at present there is too great an element of assumption" (Barcroft 1920). He went on to define three types of anoxaemia:

- 1) anoxic anoxaemia where arterial oxyhaemoglobin saturation or arterial partial pressure of oxygen, or both, are low
- 2) anaemic anoxaemia where the quantity of functional haemoglobin is subnormal
- 3) stagnant anoxaemia where tissue perfusion is inadequate.

These principles remain valid although, as Barcroft himself pointed out, the mechanisms are not necessarily mutually exclusive. In addition, interest in the possibility of an intra-cellular block to oxygen utilisation is returning, in the light of new evidence (Gutierrez 1991, Boekstegers 1994). However, Barcroft's statement that too much is left to assumption still holds true, particularly if assessment of the critically ill is based solely on clinical examination.

1.1.3. Principles of oxygen transport

The concept of whole body oxygen delivery (DO_2) as the product of cardiac output and arterial oxygen content was proposed by Richards in 1944 (Richards 1944). It is

of fundamental importance to appreciate that this measurement does not directly reflect the amount of oxygen delivered to the tissues, as any maldistribution of perfusion due to vasoderegulation will lead to arterio-venous shunting.

In normal subjects, resting oxygen consumption (VO_2) is broadly unchanged over a wide range of values of DO_2 (Cain 1967), the oxygen extraction ratio varying to maintain a stable VO_2 . The normal physiological response to a fall in DO_2 is to increase oxygen extraction. As Shibutani showed in patients anaesthetised for cardiac surgery (Shibutani 1983), this mechanism is effective until the DO_2 falls to a critical level which was 330 ml/min/m² in this and other studies (Komatsu 1987). Below this DO_2 oxygen extraction cannot increase further and VO_2 falls in parallel with DO_2 , such that there is supply dependency of VO_2 on DO_2 . Although it was originally suggested that DO_2 equated with oxygen availability, and thus the adequacy of tissue oxygenation, it is now recognised that tissue hypoxia and dysoxia may occur in the presence of a normal or high DO_2 , for the reasons outlined above.

In patients with septic shock it has long been recognised that there is impaired VO_2 which is probably due to a combination of vasoderegulation (Duff 1969), microvascular plugging (Messmer 1988) and increased capillary to mitochondrial oxygen diffusion distance (Sibbald 1989). Despite past scepticism, some

investigators are returning to the theory of direct mitochondrial dysfunction as part of the mechanism of pathological oxygen supply dependency (Boekstegers 1994), and cytokines have been implicated in this. In the normal situation, DO_2 is determined by the metabolic requirements of the tissues, with compensatory increases in DO_2 with increased VO_2 , as shown in exercise (Hermanson 1972). The concept of a threshold DO_2 below which basal VO_2 , and thus normal aerobic cellular metabolism, could not be maintained was shown by Cain in a number of elegant animal studies using anaemia, hypoxaemia, reduced cardiac output or combinations of these to depress DO_2 (Cain 1965, Cain 1967). There is accumulating evidence that in critically ill patients with sepsis, ARDS and multiple organ failure the critical threshold for delivery dependent oxygen consumption may be at normal or high levels of DO_2 (Kariman 1985, Haupt 1985, Dantzker 1991, Clarke 1991), resulting in pathological supply dependency of VO_2 on DO_2 . The use of the response of VO_2 to changes in DO_2 in an attempt to disclose tissue hypoxia is under investigation (Vincent 1990 i, Nimmo 1992). To further complicate the interpretation of whole-body oxygen transport variables there may also be abnormalities of oxy-haemoglobin dissociation, differential tissue oxygen requirements and micro-vascular dysfunction, none of which are apparent from global measurements (Ruokonen 1991).

1.1.4.

Tissue perfusion

Investigators have long sought indicators of the adequacy of tissue perfusion. Kasnitz suggested the use of mixed venous partial pressure of oxygen (PvO_2) as a guide (Kasnitz 1976) but this has subsequently been shown to be elevated or normal in septic shock patients with tissue hypoxia (Miller 1982), rendering its interpretation difficult.

The mixed venous oxy-haemoglobin saturation (SvO_2) has also been proposed as an indicator of the adequacy of tissue oxygen supply, and several studies have shown that in low flow states associated with acute myocardial infarction and with intact vasoregulation SvO_2 may have prognostic and therapeutic importance (Creamer 1990, Sumimoto 1991). However, Richards and coworkers, studying patients with chronic congestive cardiac failure, failed to demonstrate a consistent relationship between increases in DO_2 and rising SvO_2 (Richards 1989). These authors suggested that in some individuals there was an oxygen debt, which was only paid-off with the increased DO_2 . The usefulness of SvO_2 as an early marker of tissue hypoxia in vasoderegulated states remains unclear.

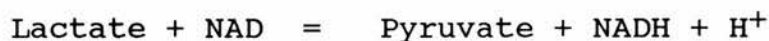
The measurement of tissue oxygen tension has been studied in both the clinical and laboratory settings. However, the clinical application of this technique, and its relevance in the critically ill remain undefined. Another proposed method of monitoring the adequacy of

regional oxygen supply is gastric tonometry. In this technique, gastric intra-mucosal pH (pHi) is calculated using measurements of the arterial bicarbonate and the pCO₂ of saline from the balloon of a tube in the gastric lumen. Conflicting opinions regarding the place pHi measurements have been expressed, and studies are necessary to define its place in the monitoring of the critically ill (Silverman 1991, Gutierrez 1992).

The pathophysiology of tissue hypoxia in critical illness is so complex and variable, both within and between subjects, that to believe in the ability to monitor the situation with a single marker is at best optimistic and at worst naive. An approach which combines the synthesised measurements from a group of appropriate monitors may be the most useful.

1.1.5. Anaerobic metabolism

Lactate is formed from pyruvate as a product of the anaerobic oxidation of glucose. Huckabee pointed out in 1958 that the cellular consequence of oxygen deficiency is the preferential shift towards the lactate dehydrogenase (LDH) system, a metabolic dead end resulting in increased lactate production (Huckabee 1958). The formation of lactate via pyruvate and its metabolism to pyruvate, catalysed by LDH can be summarised in the equation:



Huckabee postulated that if the rate of this anaerobic

metabolism could be defined, the extent of the tissue oxygen debt could be deduced. The use of lactate alone as a quantitative estimate of hypoxic anaerobiasis was questioned, as other metabolic events leading to elevated pyruvate concentrations would lead to increased lactate by virtue of the above reaction where NADH is nicotinamide adenine dinucleotide, and the enzyme controlling the reaction is LDH. The relations of the anaerobic and aerobic components of glycolysis are shown in Figure 1.

Huckabee showed that hypocapnia, hyperglycaemia and hyperpyruvataemia all resulted in hyperlactataemia, and demonstrated the utility of Excess Lactate (XL) to distinguish between non-hypoxic and hypoxic hyperlactataemia (Huckabee 1958). The XL is the fraction of lactate present in excess of that which would be expected on the basis of the prevailing pyruvate concentration, and is calculated from the equation:

$$XL = (Ln - Lo) - (Pn - Po) (Lo/Po)$$

where Ln and Lo are experimental and control (baseline) lactate concentrations, and Pn and Po are experimental and control concentrations of pyruvate, respectively. The influence of lactate removal or metabolism in these studies was not assessed, but it is widely recognised that blood lactate concentrations are higher in patients with hepatic dysfunction (Royle 1978, Kruse 1987), in experimental animals with hepatic hypoxia (Tashkin 1972) and in liver failure (Bihari 1985). This is likely to be

Lactate metabolism: Pathophysiology

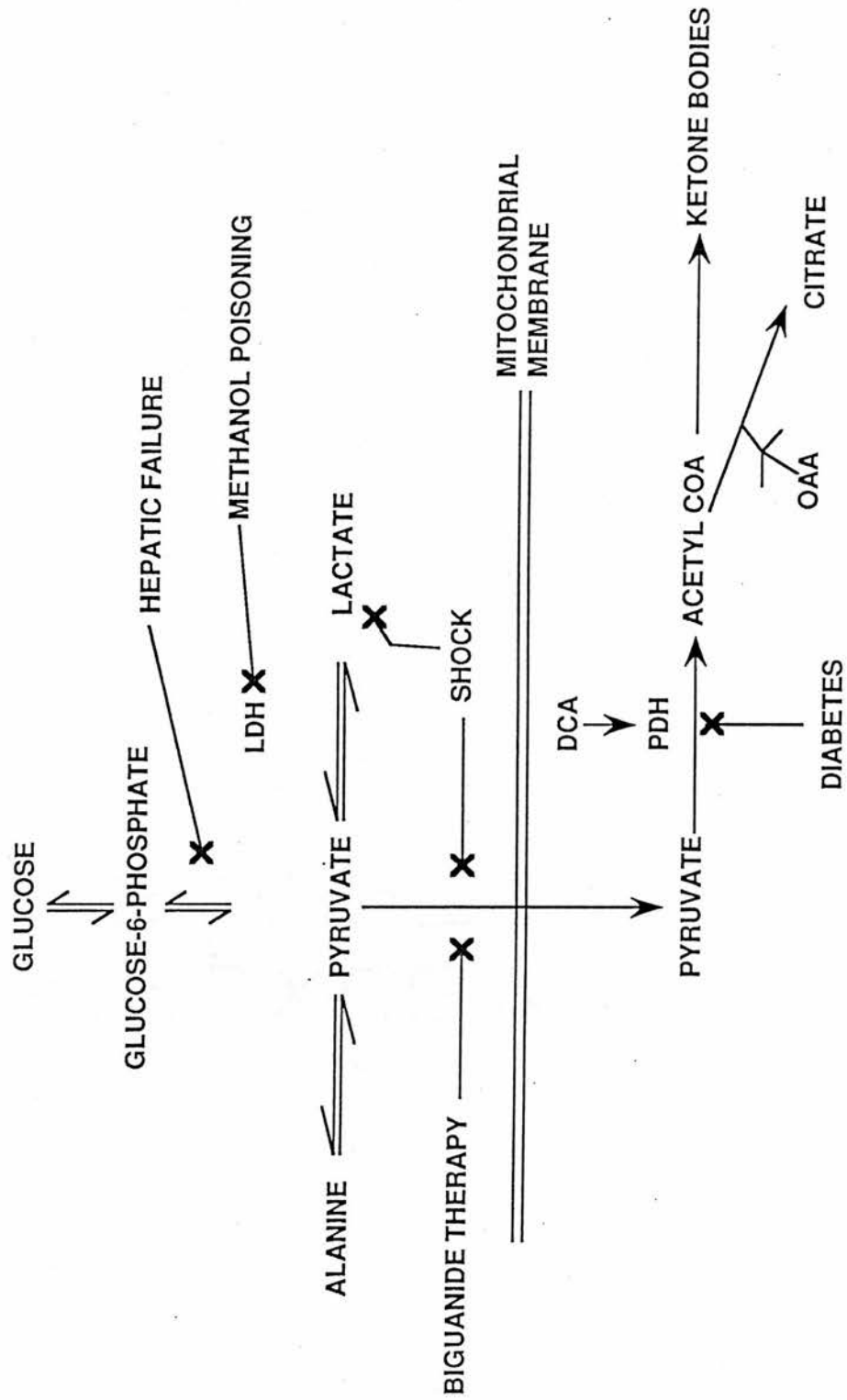


Figure 1

due to a combination of reduced clearance, and to hepatic lactate production per se.

Few clinical studies assessing the usefulness of XL have been performed, but that of Broder and Weil in 1964 supported Huckabee's findings (Broder 1964). In this study, serial XL measurements were made in 56 patients with shock of varying aetiologies. The levels of XL were found to correlate with the severity of circulatory failure, and to have prognostic value. A major impediment to the use of XL measurement in the critically ill is the lack of baseline measurements. More recently it has been suggested that the presence of significant hyperlactataemia in shock of varying aetiologies is an indicator of worse prognosis. Weil and Afifi, using a haemorrhagic rat model (Weil 1970), showed that cumulative oxygen debt correlated with log lactate. In the same paper, they presented data from 142 patients with shock, showing that lactate concentrations alone were equally good outcome predictors compared with XL values. A number of studies from the same group have confirmed these findings (Cady 1973, Shubin 1974). Other investigators and reviewers have agreed with this interpretation (Schuster 1984, Bakker 1991 i) and have further stated that the response of blood lactate to resuscitative therapy is an even better guide to outcome (Vincent 1983, Cowan 1984). On the other hand, there is some evidence that initial lactate concentrations do not have the prognostic power which has been suggested

(Shelley 1993).

1.1.6. Acid-base balance

1.1.6.1. Introduction

The development of metabolic acidosis in shock was recognised by Cannon (Cannon 1920), and had been demonstrated in a wide variety of causes of shock by Cournand and colleagues in 1943 (Cournand 1943), and again by Peretz and co-workers (Peretz 1965). Over the next 20 years the usefulness of arterial acid-base measurements became accepted as routine in the monitoring and treatment of shock and critical illness. However, it has been suggested that central or mixed venous blood gases reflect tissue metabolism much better than arterial in certain clinical situations (Weil 1987, Adroque 1989), although not in liver failure (Wendon 1991).

In critical illness the development of acid-base disturbance is often multifactorial, and the relative contributions of disturbances in the mechanisms detailed below may be difficult to assess. In shock the commonest derangement of acid-base physiology is metabolic acidosis and, as Cohen and Woods have documented, this is commonly due to hypoxic lactic acidosis (Cohen 1976).

1.1.6.2. Acid-base physiology

In normal health between 1200 and 1500 mmol of lactate with an equal number of protons is produced by

metabolically active tissues in a 70 kg human each day. Approximately 12,000 to 15,000 mmol of CO_2 is produced from the combustion of carbohydrates and fats. The CO_2 load is handled easily by the lungs with normal ventilatory effort, avoiding a potentially overwhelming acidosis. The protons produced in peripheral tissues are titrated against local blood and tissue bicarbonate along with other buffering systems, and the lactate ions are removed by the liver, kidneys and heart. The hepatic metabolism of lactate is mainly by gluconeogenesis, but also by oxidation to CO_2 and water. In either case one proton is consumed per lactate ion metabolised, resulting in the regeneration of bicarbonate in equal quantities to that lost in the original peripheral buffering, and maintaining acid-base homeostasis. Deamination of amino acids in the liver produces ammonium ions which enter the urea cycle, with the consequent production of two protons for each urea molecule. Systemic acidosis inhibits the production of urea. Oxidation of dicarboxylic and sulphur containing amino acids produces further protons, but oxidation of neutral and basic amino acids produces an almost equivalent load of HCO_3^- which balances the H^+ produced. Ammonium ions not channelled into urea synthesis are scavenged and glutamine synthetase catalyses the combination with lactate to form glutamine which is transferred to the kidneys. Protons are removed in the kidney by combination with phosphate, as ammonium ions,

by exchange for sodium ions and by direct secretion. It has been conventionally thought that glutamine is deaminated to glutamate and ammonia in the kidney, the ammonia then combining with H^+ to form ammonium. However it is now appreciated that at physiological pH the ammonium ion is formed directly. Thus in acidosis, ammonium is directed from the liver to the kidney in the form of glutamine allowing its disposal without the proton penalty incurred by urea synthesis. Cohen has suggested that the liver is the prime regulator of acid-base homeostasis, although the importance of renal bicarbonate production and recovery is undisputed (Cohen 1991).

1.2. Pathophysiology of shock

1.2.1. Cardiorespiratory variables in shock

The common pathophysiological denominator in all types of shock regardless of aetiology is imbalance between oxygen requirements and oxygen transport. This may be due to reduced or maldistributed DO_2 , increased but unfulfilled metabolic needs, an intra-cellular block to oxygen utilisation, or combinations of these factors (Mackenzie 1964, MacLean 1967, Shoemaker 1973).

1.2.2. Low flow states

In haemorrhagic shock DO_2 is reduced by the combination of low arterial oxygen content (CaO_2), mainly due to

loss of haemoglobin, and depressed cardiac output (Wiggers 1940).

The haemodynamic changes of cardiogenic shock (CS) have been well documented (Forrester 1976). In major infarcts involving the left ventricle, pump failure results in reduced stroke volume and cardiac output, with elevation of left ventricular end-diastolic pressure and hypotension. Compensatory mechanisms are activated in an attempt to maintain coronary and cerebral perfusion, and result in peripheral vasoconstriction and increased systemic vascular resistance. In contrast to the large volume of laboratory and clinical studies on haemodynamics in CS, the effects on oxygen transport have only recently been described in detail. Muir and colleagues described the relationship between SvO_2 and cardiac output in myocardial infarction (Muir 1970). Da-Luz and co-workers documented the finding of a critically low SvO_2 in CS (Da Luz 1975). In a study detailing the oxygen transport changes of CS, Creamer and colleagues demonstrated that compensatory mechanisms exist which maintain oxygen consumption despite depressed DO_2 in this condition (Creamer 1990). They showed that VO_2 remained normal at the expense of markedly increased oxygen extraction, resulting in profoundly low levels of SvO_2 . The prognostic importance of SvO_2 in acute myocardial infarction (AMI) has been highlighted by Sumimoto (Sumimoto 1991), and its potential as an important pathophysiological monitor has

been proposed (Gore 1984, Nightingale 1990).

In cardiogenic shock the fall in DO_2 is due not only to low cardiac output secondary to reduced stroke volume and left ventricular stroke work index, but also to low CaO_2 . The drop in CaO_2 is mediated by arterial hypoxaemia which may be present even in the absence of a critically elevated pulmonary artery occlusion (wedge) pressure (PAOP) and pulmonary oedema (Da Luz 1975, Edwards 1986). The arterial hypoxaemia is worsened by the increased arterio-venous admixture present with pulmonary oedema, and by the depressed CvO_2 and SvO_2 . There may be increased metabolic demands, particularly in the respiratory muscles as they attempt to maintain oxygenation and normocarbida in the face of increased work of breathing and reduced compliance. It has been shown experimentally that the terminal event in CS is often respiratory arrest due to diaphragmatic fatigue, rather than a primary cardiac event (Aubier 1982).

In both cardiogenic shock (Da Luz 1975) and haemorrhagic shock (Edwards 1988, Rady 1991) there is an increase in oxygen extraction in an attempt to maintain an adequate VO_2 . As described above, this seemingly beneficial response results in critical reductions in SvO_2 , sometimes as low as 25%, with the consequence that even in the presence of intact vasoregulation some cells at the distal end of the microcirculation will receive blood containing little or no extractable oxygen. Unless the defect of tissue oxygen delivery is rectified

cellular dysfunction becomes irreversible and ultimately cell death will result.

1.2.3. Septic shock

1.2.3.1. Introduction

As causes of morbidity and mortality, septicaemia and septic shock (SS) have become increasingly recognised over the last 40 years. Gram-negative bacteraemia (other than salmonella) was thought to be rare until the work of Waisbren, who in 1951 reported 29 cases of gram-negative septicaemia, heralding the acceptance of these organisms as major pathogens (Waisbren 1951). Although the terms gram-negative, endotoxic and septic shock are commonly used interchangeably, the latter is preferable since the others are quite specific, and the syndrome is not restricted to gram negative organisms. The relative contribution of endotoxin to the cardiorespiratory changes is difficult to gauge in clinical practice.

1.2.3.2. Pathophysiology

The syndrome of SS is produced by the interaction of a complex of distinct but linked mechanisms which result in hypoxaemia, hypovolaemia, myocardial depression, systemic vasodilatation, pulmonary hypertension and impaired tissue oxygen extraction. These changes may be due either to the direct action of the micro-organisms

or their products, or to the effects of cellular or mediator system activation which the infection provokes. These interactions are represented diagrammatically in Figures 2 and 3. Figure 3 also includes an overview of current therapeutic options, as detailed below. The importance of the distinction between the effects of the organism or the effects of mediator activation lies in the fact that eradication of the infection may not produce reversal of the sepsis syndrome (Bone 1987), with the continuing effects of an ongoing 'auto-inflammatory' response.

The presence of arterial hypoxaemia has long been recognised as an early finding in SS (Maclean 1967, Shoemaker 1973), and accompanies the tachypnoea which occurs at an early stage of the disease. The decline in arterial pO_2 is a consequence of a number of mechanisms, but an increase in pulmonary venous admixture will occur as a result of combinations of atelectasis, pneumonia, ARDS and mediator induced vascular shunting. It is in the nature of the disease process, and its causes, that most patients with SS will have intra-vascular volume depletion consequent to fluid losses from combinations of fever, excess gastro-intestinal secretions, intra-abdominal collections and bleeding. The generalised capillary leak seen in SS is probably initially mediated by kinins (Colman 1977, Cumming 1992 i) and subsequently by

PATHOPHYSIOLOGY OF SEPTIC SHOCK

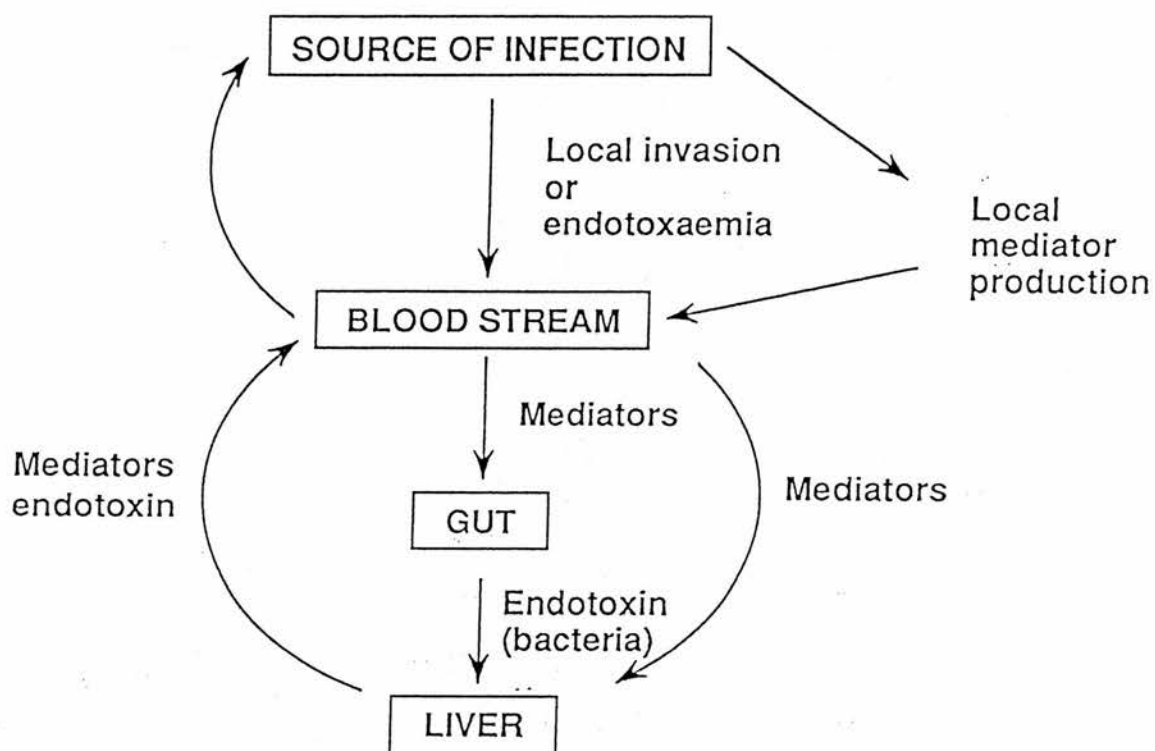
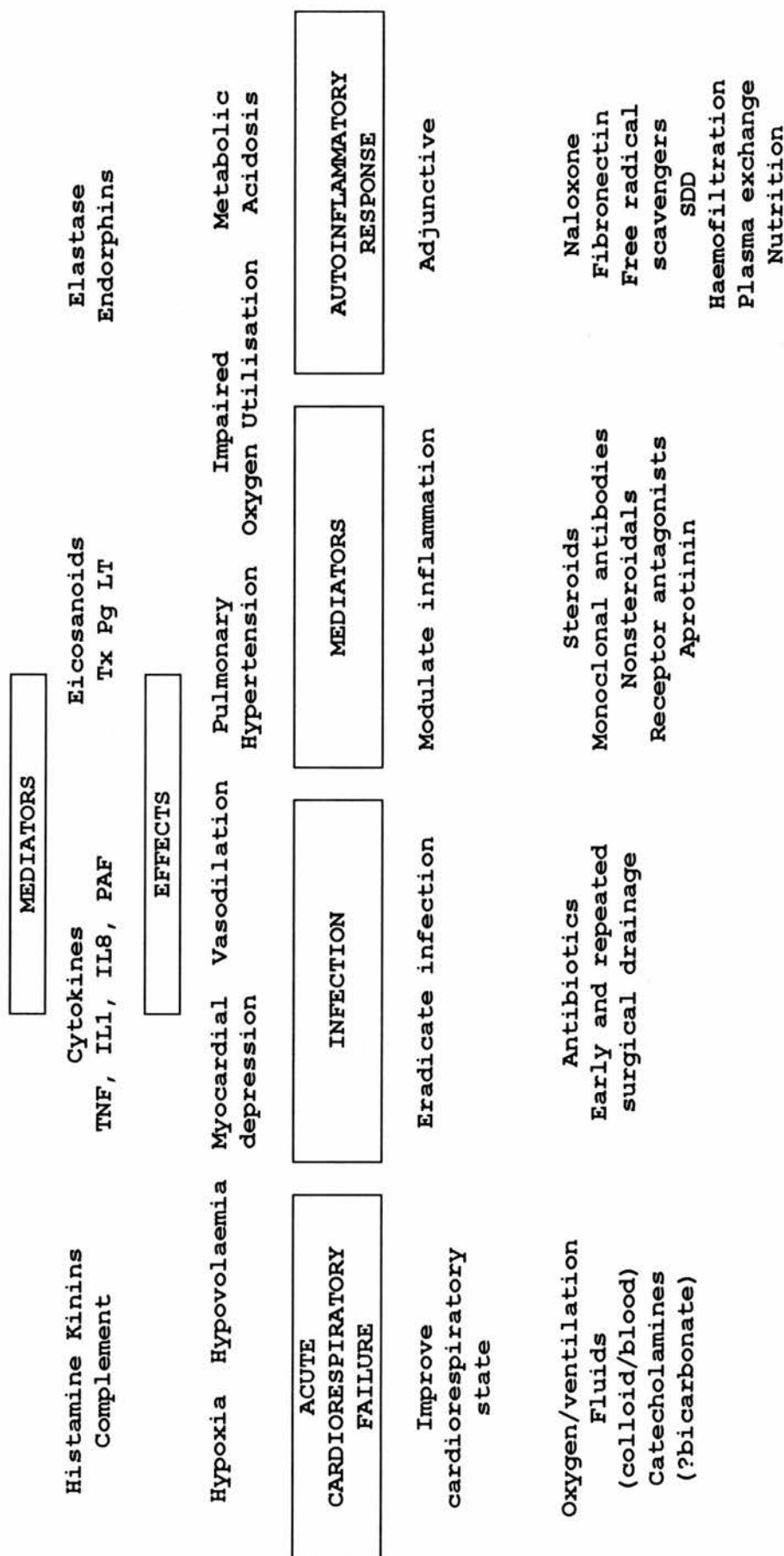


Figure 2

Figure 3 PATHOPHYSIOLOGY AND THERAPY OF SEPTIC SHOCK



cytokines, in particular interleukins. There is loss of protein and fluid from the circulation even in the presence of a normal colloid osmotic pressure. This absolute hypovolaemia is compounded by systemic vasodilatation, which by increasing the effective intra-vascular space causes relative hypovolaemia. One of the earliest haemodynamic changes in SS, systemic vasodilatation often goes unrecognised as the fall in systemic vascular resistance (SVR) is usually accompanied, at least initially, by an increase in cardiac output with consequent maintenance of blood pressure (Astiz 1987). The initial vasodilatation is probably due to endotoxin mediated activation of the plasma kallikrein-kinin system and the generation of potent vasodilator kinins as demonstrated by Mason and colleagues (Mason 1970, Robinson 1975). A number of cytokines such as Tumour Necrosis Factor (TNF) have been shown to have similar effects, and to be present in abnormally high concentrations in SS (Beutler 1987). It is unusual to find a low or low normal cardiac output in SS once hypoxaemia and hypovolaemia have been adequately corrected, most patients having high cardiac output. The original haemodynamic studies on septic shock from Detroit (Wilson 1965) and Montreal (MacLean 1967) also demonstrated that the nature of the cardiovascular response is unrelated to the type of infecting organism, a fact which appears to have been 'rediscovered' (Ahmed 1991). Despite the high cardiac

output, myocardial depression is now recognised as a major feature of the disease. Absolute myocardial depression with a low cardiac output is occasionally seen in patients with severe underlying cardiac disease or a profound intra-abdominal catastrophe such as infarcted bowel (MacLean 1967) but in the majority, following volume loading, the circulation is hyperdynamic with a low SVR and high cardiac output. It seems paradoxical, but in hyperdynamic SS with a high cardiac output severe myocardial depression can be demonstrated. Elegant studies in both animals and humans using radionuclide ventriculography have shown that both right and left ventricular ejection fractions are profoundly, although reversibly, depressed (Ognibene 1988). Parillo and colleagues have demonstrated that the high cardiac output is attained by ventricular dilatation with maintained stroke volume and an increase in heart rate (Parker 1984). This depression of myocardial contractility is likely to be multi-factorial in aetiology. The existence of a circulating myocardial depressant factor is now widely accepted, and several of the cytokines are leading contenders for this role (Parillo 1985). The significance of myocardial oedema is still under investigation (Elkins 1973, Cunnion 1986). The thromboxane and kinin mediated pulmonary hypertension of SS will aggravate right ventricular dysfunction directly (Reines 1982), and may affect the left ventricle via septal motion abnormalities as a

result of ventricular interaction.

In the midst of these abnormalities normal cellular function is further compromised by the impairment of oxygen utilisation discussed above (Duff 1969). The finding of a narrowed arterio-venous oxygen difference in SS in the presence of a high cardiac output and oxygen delivery, but with lactic acidosis suggesting ongoing tissue hypoxia, has been confirmed by other groups. Many theories have been proposed to explain this phenomenon, but it is likely to result from a number of co-existent mechanisms.

Mediator activation and cytokine release cause vasoderegulation, such that appropriate redistribution of tissue blood flow as dictated by local metabolic needs and effected by alterations in the balance of vasoconstriction and vasodilatation is impaired. Recently it has been shown that widespread oedema affects many tissues and organs in SS, at least in part due to the capillary leak mentioned above. This peri-vascular oedema will result in an increased capillary to cell diffusion distance for oxygen. At the present time, it seems that these are the two main local mechanisms interacting to cause defective oxygen consumption. However, as mentioned previously, the possibility of an intra-cellular block to oxygen utilisation is under investigation (Gutierrez 1991, Harkema 1990).

1.2.3.3.

Mediators of septic shock

In the preceeding pathophysiological description of SS the pivotal role of mediator systems in the syndrome is highlighted. The initial sequence of events which triggers the systemic responses to sepsis is complex although bacterial cell wall products including endotoxin are thought to be common initiators (Glauser 1991, Cohen 1991). Bacterial endotoxins are potent activators of the contact system and inflammatory cells, intravenous administration causing a syndrome of SS with fever and hypotension in animals and humans alike (McCabe 1971, Suffredini 1989).

The plasma contact systems are activated via Hageman factor, with subsequent activation of the kallikrein-kinin axis, the complement cascade and the fibrinolytic system. Histamine release also occurs early in SS and may contribute to vasodilatation. Activated elements of the complement cascade result in the generation of a variety of eicosanoids, and their actions contribute to the cardio-respiratory changes of SS. Thromboxane A₂ causes pulmonary vasoconstriction, and leucocyte/platelet aggregation will cause capillary plugging leading to a worsening of the imbalance in nutrient blood flow. Prostacyclin, the natural antagonist to thromboxane, may appear in excessive quantities in SS and contribute to vasodilatation and vasoderegulation. The leukotrienes also promote neutrophil adhesion, superoxide generation and may

depress myocardial contractility.

The pathophysiology of septic shock and its treatment have been reviewed in detail, with particular emphasis on the place of immuno-mediator cascades in the development of the syndrome, and on the therapeutic potential of immunotherapy (Cohen 1991).

1.2.3.4. Clinical features

As stated above the clinical and haemodynamic syndrome of septic shock can result from infection with a wide variety of micro-organisms, including gram-positive bacteria, fungi and protozoa. Shock is a syndrome in which the cardiorespiratory system fails to deliver sufficient oxygen to the tissues to maintain normal aerobic metabolism and cellular function. If this situation persists uncorrected, hypotension and organ dysfunction will result. Rapid and efficient correction of this oxygen supply/demand imbalance should reverse functional organ failures, but if prolonged tissue hypoxia has occurred then morphological damage to the cells is evident, with cell death in extreme cases. The diagnosis of septic shock (SS) is often made at a relatively late stage, once circulatory decompensation is manifested by hypotension. The basis of clinical diagnosis is the presence of hypotension and organ dysfunction in the presence of an infective focus and/or positive cultures.

The clinical, haemodynamic and metabolic findings in

septic shock are the result of the complex pathophysiological response previously detailed. In many patients with septicaemia prompt eradication of infection in conjunction with active, basic cardiorespiratory support using oxygen and volume expansion will result in improvement. However in those where this is not the case, when infection is difficult to eradicate, the organism is extremely virulent or mediator activation is overwhelming, intensive care is necessary. Assisted ventilation, invasive haemodynamic monitoring and vasoactive drug support will be required with the aim of optimising cardiorespiratory function in an attempt to restore adequate tissue oxygen delivery (Abraham 1983, Edwards 1989 i). Manipulations of the sepsis triggered auto-inflammatory process using immunotherapy or other adjunctive techniques offer further therapeutic possibilities.

1.3. Adult Respiratory Distress Syndrome

1.3.1. Pathophysiology

When ARDS was originally described by Ashbaugh and Petty (Ashbaugh 1967) it was thought to be a predominantly pulmonary problem, that is the association of hypoxaemia refractory to oxygen therapy with non-cardiogenic pulmonary oedema, in the setting of a recognised predisposing condition. It is now clear that ARDS is an inflammatory condition with multi-system involvement

similar to the systemic response to sepsis, both in the derangements of physiology and in the mechanisms involved.

The risk factors for the development of ARDS are well known, and listed in Table 1 (Fowler 1983). From what has been stated above, it is not surprising that the sepsis syndrome, shock and multiple trauma are the commonest causes. The criteria for diagnosis vary, but Murray has suggested a scoring/diagnostic system which if adopted could help clarify diagnosis and severity (Murray 1988).

The major pulmonary abnormality in ARDS is diffuse injury to the lung's alveolo-capillary barrier with resulting pulmonary oedema due to increased permeability. In addition there is acute pulmonary hypertension (PHT), as in septicaemia, and bronchospasm. The major extra-pulmonary finding is the aforementioned defect in efficient oxygen utilisation in the peripheral microcirculation, which is similar to that seen in septic shock (Cain 1991). It is currently thought that these responses are due to the activation of a major host-response including the contact systems, kinins, arachidonic acid products and cytokines. A number of investigators including Snapper (Snapper 1983) have shown that many of the features of ARDS can be induced by the administration of endotoxin, and have proposed that bronchoconstriction may be mediated by thromboxane A₂, and PHT by thromboxane B₂. It has been suggested

Table 1.

Risk factors for adult respiratory distress syndrome

Direct Injury		Indirect Injury
Pneumonia	: bacterial	systemic sepsis
	viral	shock of any cause
	legionella	non-thoracic trauma
Chest trauma	: contusion	pancreatitis
Aspiration	: gastric juice	blood transfusion
	smoke	post cardio-pulmonary bypass
	chemicals	neurogenic pulmonary oedema
	drowning	
Emboli	: amniotic fluid	Drugs : heroin
	fat embolism	paraquat
		aspirin

that the PHT in septic shock may be due to kinins (Cumming 1992 i). The importance of PHT in ARDS is highlighted by the studies of Sibbald (Sibbald 1978). The peripheral defect of oxygen utilisation in ARDS is linked to the generalised capillary damage which occurs with the initiation of the disease process. There is a whole body capillary leak syndrome, mirroring the events in the lungs, which helps explain the high incidence of extra-thoracic organ failures seen in the condition. The same mediators as in septic shock are thought to be implicated in ARDS, and these are discussed in section 1.2.3.

1.4. Principles and Practice of Therapy in Shock and Critical Illness

1.4.1. Introduction

The treatment of specific disease states necessitating intensive care will vary to some extent depending on the underlying diagnosis. However, the basic principles of therapy in intensive care are universally applicable across the diagnostic range. The main components of management include resuscitation, organ support, patient comfort, specific diagnostic investigations, specific interventions and nutrition. These broad categories are complimentary and overlapping, and it is clear that in many cases several of the strategies will be proceeding simultaneously.

1.4.2.

Resuscitation

Resuscitation in the critically ill follows the fundamental sequence of 'airway, breathing, circulation'. Initial treatment is directed at securing the airway and to correcting hypoxaemia. Studies by Aubier and colleagues have provided evidence that the terminal event in cardiogenic shock is profound diaphragmatic fatigue and ultimately apnoea (Aubier 1982, Roussos 1988). The institution of respiratory support must be a priority in the management of critically ill patients, not only to improve hypoxaemia but also to assist or relieve the exhausted respiratory muscles. The mode of ventilatory support chosen will be dictated by the severity and type of illness, but in all of the human studies in this thesis the patients were ventilated using either controlled mandatory ventilation (CMV) or synchronised intermittent mandatory ventilation (SIMV) with varying levels of positive end-expiratory pressure (PEEP). Oxygen therapy to achieve adequate levels of PaO_2 and SaO_2 was universally required in these patients, and many needed values of FiO_2 approaching 1.0. Ventilatory support remains the mainstay of respiratory management in general, adult intensive care, and the use of specialised techniques such as high-frequency jet ventilation, extra-corporeal membrane oxygenation or carbon dioxide removal, and intra-venous oxygenation is still controversial and non-routine.

1.4.3.

Fluid resuscitation

Although priority is given to airway control and oxygen therapy, and attention to the circulation is often deemed secondary, in many clinical situations the insertion of a large bore cannula for fluid infusion and vasoactive drug administration must parallel airway care.

Volume loading with colloid and blood is carried out in conjunction with cardiac output and PAOP measurement. A Sarnoff ventricular function relationship is constructed allowing the lowest PAOP associated with the highest left ventricular stroke work index to be found (Sarnoff 1954). The choice of fluid for resuscitation in shock, trauma and ARDS has been a matter of intense debate for many years. It has been shown by Shoemaker and others (Appel 1981, Gilbert 1986, Edwards 1989 ii) that colloid solutions and blood produce more rapid improvements in oxygen delivery than equivalent volumes of crystalloid and that these effects are maintained for much longer. The level of haemoglobin which is optimal for tissue oxygen delivery is not known, and will depend on the disease state. The ability to maintain bulk transport of oxygen must be offset against the potential detrimental effects on micro-circulatory flow of increasing the haematocrit. In those patients in whom DO_2 can be increased by elevating cardiac output, it has been suggested that the optimal haemoglobin concentration will need to be defined in the individual using

appropriate monitoring (Shoemaker 1988). In those patients with a limited ability to increase cardiac output in response to inotropic agents it may be appropriate to maintain a higher haemoglobin concentration.

1.4.4. Vasoactive drug therapy

In many patients with shock or ARDS suboptimal levels of cardiac output, oxygen delivery and blood pressure persist despite oxygenation and optimal volume loading (Edwards 1989 i, Mackenzie 1991 i, Redl-Wenzl 1993). The work of Shoemaker and colleagues showing that the maintenance or achievement of high levels of DO_2 in conjunction with normalisation of blood pressure results in considerable improvements in survival in critically ill surgical patients has highlighted the need for resuscitation based on measured physiological variables (Shoemaker 1988). Uncontrolled (Edwards 1989 i) and controlled (Tuchschmidt 1992) studies of this approach in severe septic shock have shown similar results. The achievement and maintenance of high levels of DO_2 with simultaneous reversal of hypotension improves survival. In order to achieve these cardiorespiratory 'goals' in severe septic shock and ARDS vasoactive drugs will be required, and have been used effectively in low flow states (Coffin 1965), sepsis (Talley 1969) and ARDS over many years (Gilbert 1986).

Vasoactive drugs may theoretically affect oxygen

transport in a number of ways. In diseases associated with pathological delivery dependent oxygen consumption such as ARDS and septic shock the increase in DO_2 should be accompanied by an increase in VO_2 . If, however, the patient's DO_2 is adequate to meet tissue oxygen demands and vasoregulation is intact a drug-induced rise in DO_2 would be accompanied by a fall in oxygen extraction ratio, with no change in VO_2 . Some catecholamines have unpredictable general or regional vasoconstrictive effects which may lead to tissue hypoxia by worsening maldistribution of blood flow (Talley 1969, Meadows 1988, Takala 1991, Mackenzie 1991 i). In addition, all catecholamines have the ability to increase overall metabolic oxygen requirements to some extent, and if the tissue oxygen supply is not increased by a commensurate amount, tissue hypoxia may result. Since most vasoactive drugs affect the pulmonary as well as systemic circulations, inappropriate pulmonary vasodilatation or vasoconstriction may occur and cause increases in pulmonary shunt fraction (Qs/Qt) which will affect arterial oxygenation (Jardin 1979, Shoemaker 1986). The approach to manipulation of the circulation using these agents will depend on the measured cardiovascular variables, but in general septic and ARDS patients require concurrent inotrope and vasoconstrictor therapy. This may be achieved with an ino-constrictor agent such as adrenaline (Mackenzie 1991 i) or with a combination such as dobutamine and noradrenaline (Edwards 1989 i,

Vincent 1990 ii). The latter combination has the significant benefit of titration of the individual effects, a technique described by Talley and colleagues in 1969 (Talley 1969). In patients with high filling pressures and non-critically depressed blood pressure an ino-dilator effect may be appropriate, and can be achieved with dobutamine (Vincent 1990 ii), a phospho-diesterase inhibitor such as enoximone (Vincent 1988) or a combination of the two. The effects of these agents in critically ill patients are unpredictable, and in addition to inter-individual variation there is intra-subject variation as the disease state changes. The prior correction of hypoxaemia, hypovolaemia and electrolyte abnormalities is mandatory and this combined with the use of invasive monitoring will enhance the chances of therapeutic success, and reduce the risks of serious adverse effects. The appropriate combination of vasoactive drugs for an individual patient will only be found by titration against repeated cardiorespiratory measurements (Talley 1969, Edwards 1991). There has been concern over the detrimental effects of vasoconstrictor drugs on renal function and acid-base status (Cohen 1976). There are now a number of studies showing the improvement in renal function using adrenaline or noradrenaline in hyperdynamic appropriately volume resuscitated patients (Redl-Wenzl 1993). Initial studies of the effects of these agents on acid-base status and blood lactate concentrations are contained in this

thesis.

1.4.5 **Cardiorespiratory optimisation in** **Cardiogenic Shock**

Much of the preceding text is more relevant to high flow, vasoderegulated shock than to low flow states. A detailed description of the treatment of CS is appropriate to highlight the potential differences in treating different shock states.

The aim of treatment in CS is to combine good symptom control with maximal survival whilst minimising myocardial damage. Appropriate analgesia, thrombolysis and other specific interventions, for example aspirin, are crucial in the overall management.

The specific physiological goals are to provide adequate perfusion pressure and DO_2 simultaneously, without worsening the myocardial oxygen supply/demand balance. In order to achieve this safely, 5 lead ST segment analysis is required, in conjunction with systemic and pulmonary arterial catheters to allow measurement of systemic haemodynamics and oxygen transport. Details of monitoring are contained in Chapter 2.

1.4.5.1. **Therapeutic approach**

Oxygen and ventilation

Hypoxaemia should be corrected with high flow oxygen, and consideration should be given to early paralysis and mechanical ventilation (Roussos 1988). Several

beneficial effects can be expected from this:

- 1) improved oxygenation with the ability to deliver high concentrations of oxygen, and the option of using PEEP
- 2) reduced metabolic demand with removal of the work of breathing
- 3) the redistribution of better oxygenated blood from the respiratory muscles elsewhere. In CS about 20% of the cardiac output may be required to supply the respiratory muscles, a ten-fold increase from normal (Aubier 1982).

Cardiac filling pressures

If the PAOP is low, controlled volume expansion with colloid should be instituted. The compliance of the ventricles may be low, resulting in large rises in pressure with small changes in volume, so small aliquots should be titrated against repeated measurements of cardiac output and PAOP. The correction of anaemia with blood will result in improved DO_2 with no myocardial oxygen demand penalty. If PAOP is critically elevated, vasodilators such as intravenous nitroglycerin can be used, but perfusion pressure may be further compromised.

Cardiac output and blood pressure

Correction of hypoxaemia and optimisation of PAOP may improve CO. Control of arrhythmias, particularly by electrical means, can improve CO. The use of sequential atrio-ventricular pacing has been advocated for its increased efficiency over standard ventricular pacing in certain situations (Donovan 1991). Over-drive pacing for

tachy-arrhythmias is not associated with the negative inotropic effects seen with most anti-arrhythmic drugs. Hypotension may improve with increasing CO, but vasoconstrictors or mechanical circulatory support may also be necessary. Blood pressure must be measured invasively because of the inaccuracy of cuff measurements in high SVR shock (Cohn 1967). Correction of hypokalaemia, and the administration of magnesium may have beneficial effects on arrhythmias.

Forrester and colleagues showed that survivors of AMI had a higher CO than non-survivors (Forrester 1976). On the basis of this the successful use of a therapeutic protocol involving the above measures and the use of positive inotropic drugs has been reported. Combinations of drugs are titrated to the individual haemodynamics aiming for cardiac index >2.2 l/min/m² and MAP >80 mmHg (or higher if previously hypertensive). Depending on the situation, GTN was used to lower PAOP, dobutamine to increase CO and noradrenaline to maintain MAP (Creamer 1990). In some situations adrenaline, dopamine or phospho-diesterase inhibitors may be useful (Vincent 1988). It is interesting to note, as detailed above, that in one of the original clinical studies of dopamine in shock the authors concluded that in the most critically ill patients combinations of catecholamines would be necessary to optimise flow and pressure independently, and that resuscitation should be guided by repeated measurements of invasive haemodynamics

(Talley 1969). No evidence has been produced that low dose dopamine selectively improves renal perfusion in CS independent of effects on CO or MAP. Dose response curves have not been constructed for dopamine in CS. In certain situations mechanical circulatory support such as intra-aortic balloon counterpulsation may be appropriate. The place of early coronary balloon angioplasty or revascularisation is undefined as yet.

Oxygen transport

The use of catecholamines in CS may be associated with worsening of myocardial ischaemia, by increasing contractility or heart rate. In order to use an effective dose, whilst not overtreating, the use of a target CO is useful. However, from the basic pathophysiology it is clear that SvO_2 may provide a further objective guide in titrating therapy. If vasoregulation is intact, the achievement of an SvO_2 >60% implies that DO_2 to the perfused tissues is likely to be adequate. Correction of lactic acidosis using sodium bicarbonate has no beneficial effect on cardiorespiratory function in low flow states, and some investigators have shown it to be detrimental (Bersin 1989, Cooper 1990). Until recently the therapy of CS has been largely piecemeal, with ill-defined therapeutic targets. Evidence is appearing that manipulation of the oxygen transport system may be beneficial in CS, with SvO_2 a crucial measurement.

1.4.6.

Sedation in intensive care

During resuscitation, and throughout the stay in intensive care, it is crucial that the patient is comfortable and pain-free. Communication should be continued with frequent explanation and reassurance. The majority of patients will receive a continuous low-dose opiate infusion for analgesia, and to depress the cough reflex in order to help in tolerating the endotracheal tube. These agents are often supplemented by boluses or continuous infusions of a benzodiazepine such as midazolam, or the anaesthetic induction agent propofol. The level of sedation is assessed using a linear scale, ideally aiming for a degree of sleepiness from which the patient is easily rousable into a cooperative and communicative state (Ramsay 1974). In patients who are not critically unstable but who require continued ventilatory support, such as Guillain-Barre syndrome or severe COAD, there may be no need for continuous drug administration, especially if a tracheostomy has been performed. Full neuromuscular paralysis is not necessary in the majority of patients after their initial resuscitation and stabilisation unless there is a specific indication. Deeper levels of sedation may be specifically indicated for certain disease states such as tetanus or in conditions with raised intracranial pressure. The benefits to be gained from sedation in terms of the oxygen supply demand balance have not been rigorously investigated.

1.4.7. Renal replacement therapy in the critically ill

The requirement for safe, practical and efficient renal replacement therapy (RRT) in critically ill patients with respiratory failure and haemodynamic instability has led to a search for alternatives to haemodialysis. In many of these patients the use of haemodialysis is severely limited by the hypotension (Vincent 1982) and worsening of hypoxaemia (Jones 1980) which have been documented. Alternative techniques involving haemofiltration have become popular, and may be continuous (Kramer 1983, Simpson 1987) or intermittent (Davenport 1989, Mackenzie 1991 ii). These have been shown to be well tolerated and to provide adequate biochemical control and fluid balance (Kramer 1983, Mackenzie 1991 ii). There are however theoretical concerns over the use of replacement fluids which contain lactate as the buffer source (Davenport 1989).

1.4.8. Advances in therapy: Immunomodulation

A further development in the management of critically ill patients with septic shock has been the introduction of monoclonal antibodies to cytokines such as TNF and IL6. More recently a human monoclonal antibody against endotoxin has been developed, although initial studies have been greeted with such concern that the agent has been withdrawn from clinical use (Ziegler 1991). However, there are several established, safe drugs which

may have beneficial effects on either mediator cascades or end-organ damage. These include the phospho-diesterase inhibitor pentoxifylline (Bennett 1989 ii, Tighe 1990) and non-steroidal anti-inflammatory drugs such as ibuprofen (Haupt 1991). We have chosen to study the effects of aprotinin, an agent extensively used in humans, and with a proven record of safety. The next decade should show whether these and related agents (Baumgartner 1985) offer hope of improved survival, although the mainstay of intensive therapy is likely to remain adequate, early resuscitation in combination with scrupulous supportive care. It is on the basis of this, and in an attempt to improve our understanding of currently available treatments, that the work documented in this thesis has been carried out.

2.1. Introduction

The measurement of systemic haemodynamics and whole body oxygen transport has become an integral part of the management of critically ill patients, and the techniques used are described below. Blood gas and acid-base measurements are performed routinely using standard, automated equipment and no details of this are presented here. The assays of lactate, pyruvate, kallikrein and plasma renin activity are detailed.

2.2. Overview of monitoring in the critically ill

Monitoring is used in intensive care on three levels:

1. To identify events which might trigger injury producing processes eg tachycardia in patients with coronary artery disease.
2. To quantify ongoing injurious processes eg raised intracranial pressure.
3. To assess the presence and severity of established processes eg cardiogenic shock, ARDS.

From this it can be seen that surveillance with real time monitors such as invasive blood pressure, continuous oximetry (invasive or non-invasive, arterial or mixed venous) or intracranial pressure measurement will allow the early detection of otherwise unrecognised

yet important events. This increased certainty of physiological status will only be of value if effective therapeutic interventions to modify these events are available, and appropriate endpoints have been defined and are used to guide treatment. The use of continuous electrical cerebral function monitoring combined with dual (jugular venous and systemic arterial) oximetry and intracranial pressure measurement in the monitoring of head injuries exemplifies this.

The responses of the measured variables to different therapeutic manoeuvres clarifies the pathophysiology over short periods of time and allows the appropriate choice of intervention to achieve the primary aim, that is a minimisation of secondary insults, in the above situation brain ischaemia.

The use of monitors in severe sepsis and ARDS tends to occur once there is already injury, usually with at least two organ system failures present, most commonly acute cardiorespiratory failure.

There is general agreement that in these patients the use of an indwelling arterial line and a thermodilution, flow directed pulmonary artery catheter are mandatory for assessment of pressures, flow (cardiac output) and circulatory function in terms of oxygen transport, and the subsequent titration of appropriate combinations of fluid therapy, ventilatory support and vasoactive drugs (Bennett 1991 i).

2.2.1.

Arterial access

The technique of arterial cannulation has been used for many years, and has been routine in intensive care for over 25 years. An indwelling arterial catheter allows measurement of MAP, used to calculate derived haemodynamic variables, and repeated atraumatic blood sampling. The larger and more proximal to the aorta the artery used, the more likely the waveform and pressures recorded will be similar to those of the central aorta, particularly in patients with abnormalities of blood pressure. The majority of patients in these studies had femoral arterial lines, a few having radial artery catheters. These were inserted percutaneously using the Seldinger technique (Seldinger 1953). In the ovine studies, the common carotid artery was dissected out, two silk slings were used to control it and it was cannulated under direct vision, again using the Seldinger method, the line then being advanced into the aorta.

2.2.2.

Pulmonary artery catheterisation

Percutaneous catheterisation of the right heart and pulmonary artery using a multi-lumen, balloon tipped, flow directed catheter has become a well established haemodynamic monitoring technique since its introduction over 20 years ago (Swan 1970). In the human studies access to the central veins was by the internal jugular route, into which a percutaneous 8.5 Fr introducer

(Baxter Edwards, Irvine, California) was inserted by the Seldinger technique. The external jugular vein was used in the ovine studies. A 4 lumen PAC was floated in under pressure-waveform guidance, and position was checked on chest x-ray. The catheter was used to measure pressures (CVP, MPAP, PAOP), cardiac output and for mixed venous blood sampling. Cardiac output was determined by thermodilution in triplicate using cold injectate. An in-line heat exchange coil and ice-bucket (Co-set, Baxter Edwards, Irvine, California) and in-line thermistor system were used. Dextrose 5% in 10ml boluses was injected, curves displayed and values within 5% accepted. Right ventricular ejection fraction was determined in a small group of patients, using specially modified PACs with fast-response thermistors (Ref catheters, Baxter Edwards, Irvine, California). Pressure measurements and cardiac outputs were stored by the integrated modular bedside monitor (7200 series, Marquette Electronics, Milwaukee, Wisconsin). Heart rate was measured automatically by the monitor, and using these measured variables the haemodynamic derived parameters were calculated (Table 2). Table 2 contains ranges of normal values for these parameters.

2.3. Oxygen Transport

Samples of mixed venous and arterial blood were taken for blood gas analysis within one minute of the last cardiac output. Haemoglobin concentration and arterial

Table 2 : Haemodynamic Variables - Basic Equations and Normal Values.

Mean Arterial Pressure (MAP) : 80-100 mmHg

Central Venous Pressure (CVP): 1-6 mmHg

Pulmonary Artery Occlusion Pressure (PAOP) : 4-12 mmHg

Mean Pulmonary Artery Pressure (MPAP) : 11-15 mmHg

Cardiac Output (CO) : 4-6 l/min

Cardiac Index (CI) = CO / BSA : 2.8-3.6 l/min/m²

Stroke Volume (SV) = CO / HR : 50-100 ml

Stroke Volume Index (SVI) = CI / HR : 50-70 ml/m²

Right Ventricular Ejection Fraction (RVEF) : 50-70%

Systemic Vascular Resistance (SVR) = $79.92 (MAP - CVP) / CO$
dyne.sec/cm⁵

Systemic Vascular Resistance Index (SVRI) =

$$\frac{79.92 (MAP - CVP) / CI}{2180 \pm 210} \text{ dyne.sec/cm}^5 \cdot \text{m}^2$$

Left Ventricular Stroke Work Index (LVSWI) = $SI \times MAP \times 0.0144$
50-62 g.m/m²

Right Ventricular Stroke Work Index (RVSWI) =

$$SI \times MPAP \times 0.0144$$

7.8-9.0 g.m/m²

BSA = Body Surface Area

and mixed venous oxyhaemoglobin saturations were measured using a co-oximeter (Ciba-Corning Diagnostics, Halstead, UK). The oxygen content of arterial (CaO_2) and mixed venous (CvO_2) blood, and the derived oxygen transport parameters (DO_2 , VO_2 , OER, Qs/Qt) were calculated using standard formulae. By convention cardiac output is indexed for body surface area, thus DO_2 is the indexed product of CaO_2 and cardiac index (CI). Oxygen consumption is obtained using the inverse Fick relationship:

$\text{VO}_2 = \text{CI} \times \text{arterio-venous oxygen content difference}$
(Table 3). Ranges of normal values are included in the table.

In the physiology laboratory VO_2 has traditionally been measured by analysis of expired gas using a Douglas bag. This method becomes less accurate as the inspired oxygen concentration rises, making it unsuitable for many critically ill patients.

It has been suggested that since the calculations of VO_2 and DO_2 involve shared variables, most notably CI, the finding of increases in VO_2 with increases in DO_2 may be linked mathematically rather than physiologically.

Detailed investigations have been carried out on this basis, and debate has been widespread. The fact that many studies have demonstrated the existence of groups of individuals in whom changes in VO_2 do not parallel changes in DO_2 may be sufficient to refute the validity of mathematical coupling.

Table 3 : Oxygen Transport - Basic Equations and Normal Values

$$CaO_2 \text{ (ml/dl)} = (Hb(g/dl) \times SaO_2 \times 1.39) + (PaO_2 \text{ (mmHg)} \times 0.003)$$

~ 20 ml/dl

$$CvO_2 \text{ (ml/dl)} = (Hb(g/dl) \times SvO_2 \times 1.39) + (PvO_2 \text{ (mmHg)} \times 0.003)$$

~ 15 ml/dl

$$DO_2 \text{ (ml/min/m}^2\text{)} = CI \times CaO_2 \times 10 \quad : 520-720 \text{ ml/min/m}^2$$

$$VO_2 \text{ (ml/min/m}^2\text{)} = CI \times (CaO_2 - CvO_2) \times 10 \quad : 100-180 \text{ ml/min/m}^2$$

Reverse Fick Equation

$$OER(\%) = (CaO_2 - CvO_2) / CaO_2 \quad : 22-30 \%$$

$$Qs/Qt = CcO_2 - CaO_2 / CcO_2 - CvO_2 \quad : 0-5 \%$$

CaO_2 = arterial oxygen content

CvO_2 = mixed venous oxygen content

CcO_2 = capillary oxygen content

SaO_2 = arterial haemoglobin oxygen saturation

SvO_2 = mixed venous haemoglobin oxygen saturation

PaO_2 = arterial partial pressure of oxygen

PvO_2 = mixed venous partial pressure of oxygen

OER = oxygen extraction ratio

Qs/Qt = pulmonary venous admixture

2.4. Assays used in this project

2.4.1. Lactate

2.4.1.1. Introduction

It has been suggested that lactate sampling should be from the mixed venous blood in preference to arterial. It has been demonstrated that in patients with severe pulmonary pathology arterial lactate concentrations exceed mixed venous levels as a result of lactate production in diseased lung (Rochester 1973). We examined the relationship between arterial and mixed venous whole blood lactate concentrations in critically ill patients.

It has been shown that patients suffering from lung cancer and pulmonary tuberculosis produce lactate in locally diseased areas of lung and that occasional patients have a significantly higher arterial lactate as a result (Rochester 1973). Despite this, these workers showed no overall significant arteriovenous difference in lactate concentrations in their study. However some investigators have used mixed venous samples, in preference to arterial, to measure lactate concentrations in critically ill patients (Kox 1991). We performed this study to see whether this was appropriate or necessary in intensive care patients.

2.4.1.2. Patients and methods

We studied 22 consecutive admissions to a general intensive care unit on one occasion each. The mean age

was 60 years, range 39-80. All patients were mechanically ventilated and had arterial and pulmonary artery catheters in situ for standard, clinical monitoring. Underlying diagnoses were septic shock (n=16), ARDS (n=18), severe acute left ventricular failure (n=4) and pneumonia (n=2). Some patients fell into two diagnostic groups. Arterial and mixed venous samples were drawn simultaneously into heparinised syringes and analysed as detailed below.

Statistical analysis was by the graphical method of Bland and Altman (Bland 1986) and standard correlation coefficient. The technique of Bland and Altman requires the plotting of information derived from pairs of data points, the mean of the two values being plotted against their difference. The results are expressed as bias (mean difference) and limits of agreement (mean difference \pm 2SD).

2.4.1.3. Results

The arterial lactate concentrations were 2.1 ± 0.31 mmol/l, and the mixed venous 2.0 ± 0.32 mmol/l expressed as Mean \pm SEM. The degree of correlation was excellent ($r=0.99$) as depicted in Figure 3. As shown in Figure 4 the bias was 0.09, and the limits of agreement \pm 0.38 (range -0.47 to 0.29), which are well within the range of clinically important changes in lactate concentration.

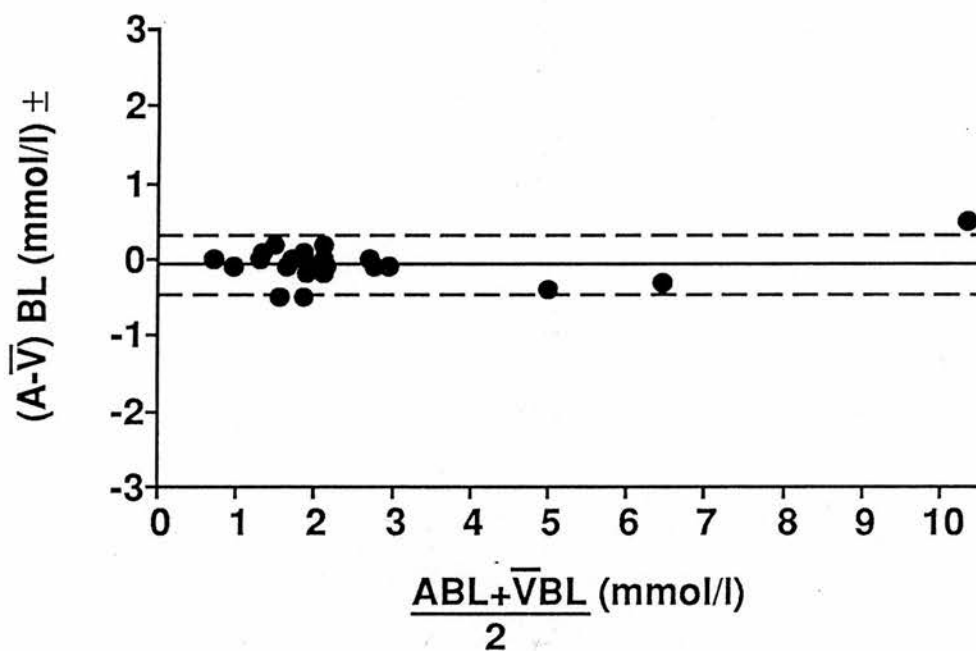


Figure 4

Arterial and mixed venous lactate : Bland and Altman plot



2.4.1.4.

Discussion

Rochester and colleagues demonstrated the potential for diseased lung to produce lactate (Rochester 1973). They concluded that this was a reflection of increased lung metabolism and speculated that the degree of arteriovenous difference in lactate might reflect the extent of diseased lung. We have been unable to demonstrate any difference between arterial and mixed venous lactate in a group of critically ill patients with much higher mean lactate concentrations than in the Rochester study, and with quite different pathology. It would appear from these results that arterial lactate concentration is at least as useful as mixed venous in these patients. It is also of interest to note that those investigators who have suggested levels of lactate which might be deemed significant have used arterial measurements (Weil 1970, Groeneveld 1987). Arterial sampling for blood lactate determination is clinically and experimentally relevant and practical.

2.4.2

Lactate measurement

Arterial blood samples were drawn, and 1.5 ml placed into pre-weighed glass tubes containing 5 ml of cold (4°C) 5% perchloric acid, immediately refrigerated and subsequently analysed. The principle of the technique involves the conversion of lactate to pyruvate in the presence of LDH and NAD, the buffer pH driving the reaction in favour of lactate oxidation. Lactate was

measured using a Cobas Bio (Roche) centrifugal analyser, monitoring the rate of reduction of NAD to NADH fluorimetrically at an excitation wavelength of 340 nm in 0.5M glycine buffer (pH 9.6) in the presence of .2M hydrazine tartrate and lactate dehydrogenase. Lactate standards from 50-1200 $\mu\text{mol/l}$ were used. Whole blood lactate was then calculated after correcting for dilution of the sample with 5% perchloric acid. Interassay C.V. over the working range is <10%.

2.4.3. Pyruvate measurement

Samples were those collected as above, and used for lactate measurement. Pyruvate was measured using the Cobas Bio centrifugal analyser with fluorimetric attachment, as described above. The principle of the assay is the conversion of pyruvate to lactate in the presence of NADH. Interassay C.V. over the working range is <10%.

2.4.4. Urinary kallikrein

This was measured by the method of Amundsen et al (Amundsen 1979). This assay has been validated by comparison with measurement of urinary kininogenase activity using a kinin radioimmunoassay (Bonner 1981). Urine for kallikrein estimations was taken directly into plastic containers, and frozen at -20°C after a maximum of 24 hrs at room temperature. Samples were thawed at 20°C , and centrifuged prior to assay; all samples were

assayed within 4 hrs of thawing.

Urinary kallikrein was measured using the chromogenic substrate S-2266 (H-D-Val-Leu-Arg-pNA) (AB Kabi Diagnostica). A Tris buffer, pH 8.2, was prepared as detailed elsewhere (Cumming 1989 i).

A Trasylol (lyophilised aprotinin, Bayer, FRG) buffer was prepared to a concentration of 20 KIU/ml. This was added to a sample blank for each assay. Since aprotinin is a potent inhibitor of urinary kallikrein, but does not inhibit urokinase, the only other alkaline esterase enzyme in urine, subtraction of the result of this blank from the sample value increased the specificity of the assay, in addition to correcting for the intrinsic urine colour.

Determination of urinary kallikrein

H-D-Val-Leu-Arg-pNA + H₂O---urinary kallikrein---peptide + pNA

500 ul of buffer at 37°C was added to 400 ul urine and incubated at 37°C for 5 minutes. 100 ul of S-2266 was added and incubated for 30 minutes. The reaction was then stopped by addition of 100 ul of 50% acetic acid. A sample blank was prepared, identical other than the use of aprotinin buffer. The absorbance of each sample was read against its blank at 405 nm. Results were expressed as nkat/l, one nkat being the amount of glandular kallikrein which cleaves 0.05 umol of substrate per minute under the given conditions. This was calculated as $\text{nkat/l} = 146 \times \text{absorbance}$.

Urinary kallikrein was stable at -20°C for up to one year; all samples were assayed within 3 months. Interassay CV was 8.2%, intraassay CV 4.5%.

2.4.5. Plasma renin activity

Plasma renin activity was measured by radioimmunoassay (Haber 1969).

3.1. Introduction

An elevated blood lactate concentration in clinical shock has traditionally been said to indicate a grave prognosis whatever the underlying aetiology (Mackenzie 1964, Peretz 1965, Weil 1970). However, arterial blood lactate (ABL) is not universally measured as a routine in acutely ill patients. One of the reasons for this is the potential difficulty in interpretation of elevated blood lactate concentrations because of a number of factors apart from tissue hypoxia which may result in hyperlactataemia. These and the fact that the measured ABL concentration reflects the balance between production due to tissue hypoxia and other factors, and its clearance (Cohen 1976), notably by the liver (Royle 1978), complicate the interpretation of high ABL. In an attempt to improve the usefulness of lactate measurement, and to unravel the pathophysiology of lactic acidosis, detailed animal studies investigating the serial relationship between DO_2 , VO_2 and ABL have been conducted. Many are confined to hypoxic, haemorrhagic (Cain 1965, Cain 1991), and endotoxin (Blair 1971) models, and until recently there were relatively few clinical studies. The use of serial measurements allows more accurate

prediction of outcome (Vincent 1983, Cowan 1984) but even their value has been undermined by the proposal that a "lactate wash-out" phenomenon may occur (Cohen 1976, Puri 1980). It has been hypothesised that improved perfusion of previously hypoxic tissues as a result of successful resuscitation may cause a rising ABL concentration in a similar manner to that demonstrated following exercise in animals and humans (Hermanson 1972, Zapol 1987). It is suggested that this occurs as a result of improved tissue perfusion rather than because of persisting or worsening tissue hypoxia. Experimental work has produced conflicting results (Puri 1980, Falk 1985) but the phenomenon of lactate washout has yet to be convincingly demonstrated in clinical shock. In this study the relationships between serial measurements of oxygen transport variables and ABL in a consecutive series of 40 patients with shock of diverse aetiologies were examined.

3.2. Patients and methods

3.2.1. Patients

Forty critically ill patients (mean age 61.4, range 19-80) admitted to one of two intensive care units who required immediate haemodynamic monitoring, and in whom serial ABL measurements were performed, were studied. The clinical details of this heterogeneous group of surgical and medical patients are given in Table 4.

Table 4

Clinical Characteristics of Patients.

	Age - Years (mean \pm SD)	Apache II (mean \pm SD)	Septic Shock	Cardiogenic Shock	Other
Group I	61 \pm 22	23.4 \pm 5.7	13	5	2
Group II	58.4 \pm 9.6	16.5 \pm 6.7	8	5	1
Group III	56.9 \pm 9.6	22.7 \pm 8.8	7	0	0

Patients were excluded if they had additional reasons for hyperlactataemia. Those with hyperglycaemia, known liver disease, or who had received catecholamines or any other pharmacological support of the circulation prior to initial measurements were therefore excluded. No patient received sodium bicarbonate or any other buffer before or during the study period.

3.2.2. Protocol

All patients were invasively monitored as detailed in Chapter 2. Simultaneous samples of arterial and mixed venous blood were taken and oxygen tensions, haemoglobin concentration and oxy-haemoglobin saturations measured. Arterial and mixed venous oxygen contents, VO_2 , DO_2 and oxygen extraction ratio (OER) were calculated from the standard formulae (Methods: Table 3). Cardiac output was indexed to body surface area which was determined from standard nomograms and measurements of height and weight. Serial measurements of oxygen transport variables and ABL concentration were made as clinically indicated during resuscitation.

3.2.3. Resuscitation

Standardised resuscitation protocols were used in all patients. In those patients with septic shock, ARDS and trauma the aim of therapy was to reverse hypotension and maintain high CI and DO_2 concurrently. Following correction of hypoxaemia with high inspired oxygen

concentrations, tracheal intubation and ventilation, controlled volume expansion was performed with colloid and blood. Once the PAOP had reached 15 mmHg or the left ventricular stroke work index had stopped rising in response to fluid infusion, vasoactive drug therapy was started. The choice of catecholamine was dependent on the haemodynamic profile after volume administration, and combinations of inotrope (dobutamine), vasoconstrictor (noradrenaline) and inoconstrictors (adrenaline, dopamine) were used to aim for previously defined cardiorespiratory therapeutic goals of $CI >4.5 \text{ l/min/m}^2$, $DO_2 >600 \text{ ml/min/m}^2$ and $MAP >80 \text{ mmHg}$. In the patients with cardiogenic shock more appropriate physiological endpoints were the goals of therapy. After initial correction of hypoxaemia and optimisation of cardiac filling pressures, inotropic therapy was titrated against cardiac output and SvO_2 aiming for $CI >2.2 \text{ l/min/m}^2$; $SvO_2 >60\%$; $MAP >80 \text{ mmHg}$. There is no consensus on the threshold level of hyperlactataemia which is clinically significant (Peretz 1965, Weil 1970), and the effects of factors which alter metabolic rate and thus oxygen demand on this threshold are currently under investigation. It is clear however that changes in body temperature, sedation, paralysis and assisted ventilation in most modes may alter the oxygen supply/demand relationship (Aubier 1982, Lister 1991). In this study a threshold value of 1.5 mmol/l was chosen in accordance with other investigators (Peretz

1965). Acute Physiology and Chronic Health Evaluation scores (APACHE II) were recorded in each unit (Knaus 1985), and as in the other clinical studies detailed in this thesis that documented here is the worst in the first 24 hours.

3.2.4. Statistical analysis

All results are expressed as mean \pm SEM. The paired data obtained before and after resuscitation were compared with the Wilcoxon signed rank test, and differences were considered significant at $p < 0.05$.

3.3. Results

Three groups of patients could be identified according to their initial or subsequent ABL concentrations.

Patients in Group I ($n=20$) had elevated ABL, mean 3.3 ± 0.4 mmol/l which fell to 1.5 ± 0.2 mmol/l in response to successful resuscitation, as evidenced by a rise in MAP from 65 ± 3 mmHg to 82 ± 3 mmHg with a concurrent increase in DO_2 from 435 ± 52 ml/min/m² to 600 ± 46 ml/min/m². Eight of these patients survived.

Group II patients ($n=14$) had elevated ABL levels, mean 3.2 ± 0.8 mmol/l which increased significantly to 3.9 ± 0.6 mmol/l despite active resuscitation. MAP rose from 63 ± 4 mmHg to 77 ± 6 mmHg, but there was an insignificant change in DO_2 from 499 ± 58 ml/min/m² to 568 ± 68 ml/min/m². Only two of these patients survived,

and they both had low Apache II scores of 3.

Group III patients (n=6) had ABL concentrations of less than 1 mmol/l throughout the course of the study, mean 0.7 ± 0.1 mmol/l, despite simultaneous clinical and cardiorespiratory features of shock. All of these patients survived.

The haemodynamics, oxygen transport variables and ABL levels before and after resuscitation in each group are shown in Table 5, and results are depicted in Figures 5, 6 and 7.

In summary, in Group I there were increases in blood pressure, CI, DO_2 , SvO_2 with decreases in OER. In Group II although blood pressure increased, there were no concurrent improvements in other haemodynamic or oxygen transport variables and there was a tendency to increasing ABL concentrations. In Group III there were significant increases in MAP, CI and DO_2 with significant falls in OER leading to increases in SvO_2 .

3.4. Discussion

The relationship of the cardiorespiratory variables and ABL in hypoxia, hypovolaemia and shock has been comprehensively documented in a number of elegant laboratory experiments (Cain 1965, Cain 1967). Following on from this the clinical studies of Maclean and colleagues (Maclean 1967) demonstrated that in hyperlactataemic septic shock patients who responded to resuscitative therapy with falls in lactate, there was a

Table 5 : A Summary of Haemodynamic and Oxygen Transport Variables

	Group 1				Group 2				Group 3			
	A	B	p	A	B	p	A	B	A	B	p	p
MAP (mmHg)	65 ⁺ / ₋₃	82 ⁺ / ₋₃	<0.001	63 ⁺ / ₋₄	77 ⁺ / ₋₆	<0.05	54 ⁺ / ₋₄	80 ⁺ / ₋₄	54 ⁺ / ₋₄	80 ⁺ / ₋₄	<0.01	<0.01
CI (ml/min/m ²)	2.8 ⁺ / _{-0.3}	3.9 ⁺ / _{-0.3}	<0.001	3.1 ⁺ / _{-0.4}	3.6 ⁺ / _{-0.4}	NS	3.1 ⁺ / _{-0.5}	4 ⁺ / _{-0.2}	3.1 ⁺ / _{-0.5}	4 ⁺ / _{-0.2}	NS	NS
SvO ₂ (%)	64 ⁺ / ₋₃	75 ⁺ / ₋₂	<0.01	70 ⁺ / ₋₃	70 ⁺ / ₋₃	NS	73 ⁺ / ₋₃	77 ⁺ / ₋₃	73 ⁺ / ₋₃	77 ⁺ / ₋₃	NS	NS
DO ₂ (ml/min/m ²)	435 ⁺ / ₋₅₂	600 ⁺ / ₋₄₆	<0.05	499 ⁺ / ₋₅₈	568 ⁺ / ₋₆₈	NS	413 ⁺ / ₋₄₂	672 ⁺ / ₋₄₁	413 ⁺ / ₋₄₂	672 ⁺ / ₋₄₁	<0.01	<0.01
VO ₂ (ml/min/m ²)	125 ⁺ / ₋₉	133 ⁺ / ₋₅	NS	128 ⁺ / ₋₁₀	140 ⁺ / ₋₁₁	NS	111 ⁺ / ₋₈	118 ⁺ / ₋₁₁	111 ⁺ / ₋₈	118 ⁺ / ₋₁₁	NS	NS
OER (%)	34 ⁺ / ₋₃	25 ⁺ / ₋₂	<0.05	28 ⁺ / ₋₃	29 ⁺ / ₋₃	NS	27 ⁺ / ₋₂	16 ⁺ / ₋₃	27 ⁺ / ₋₂	16 ⁺ / ₋₃	<0.05	<0.05
ABL (mmol/l)	3.3 ⁺ / _{-0.4}	1.5 ⁺ / _{-0.2}	<0.001	3.2 ⁺ / _{-0.8}	3.9 ⁺ / _{-0.6}	<0.05	0.7 ⁺ / _{-0.1}	0.4 ⁺ / _{-0.1}	0.7 ⁺ / _{-0.1}	0.4 ⁺ / _{-0.1}	NS	NS

A = initial measurements ; B = final measurements

Changes in oxygen transport and lactate during shock Group 1 (n=20)

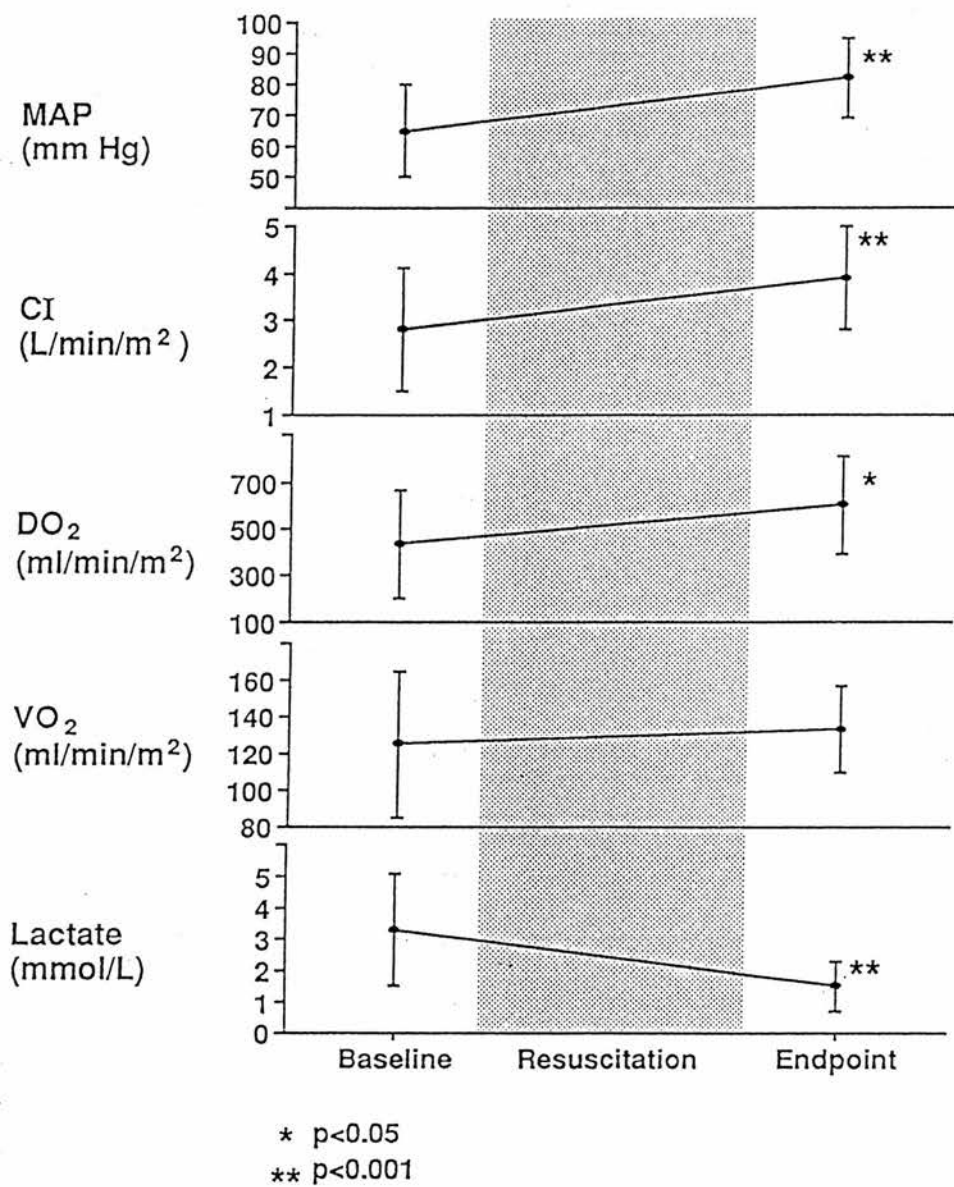


Figure 5

Changes in oxygen transport and lactate during shock
Group 2 (n=14)

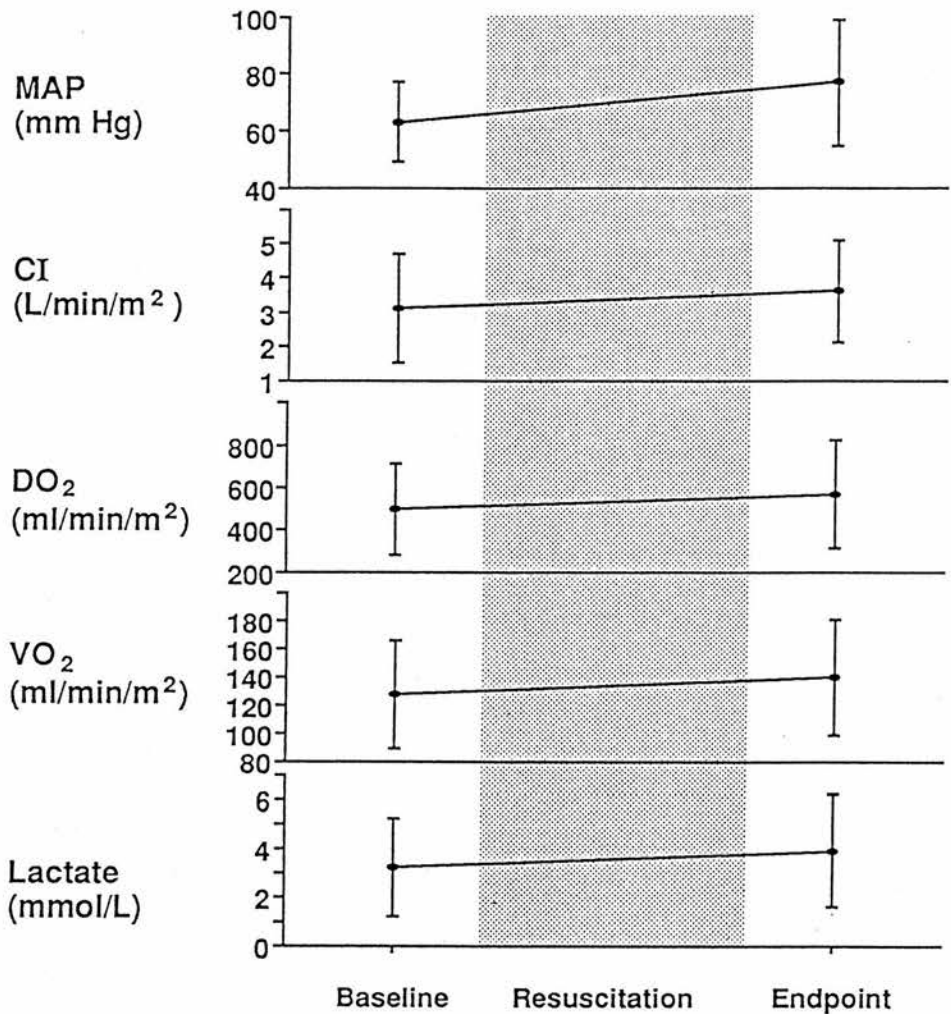


Figure 6

Changes in oxygen transport and lactate during shock
Group 3 (n=6)

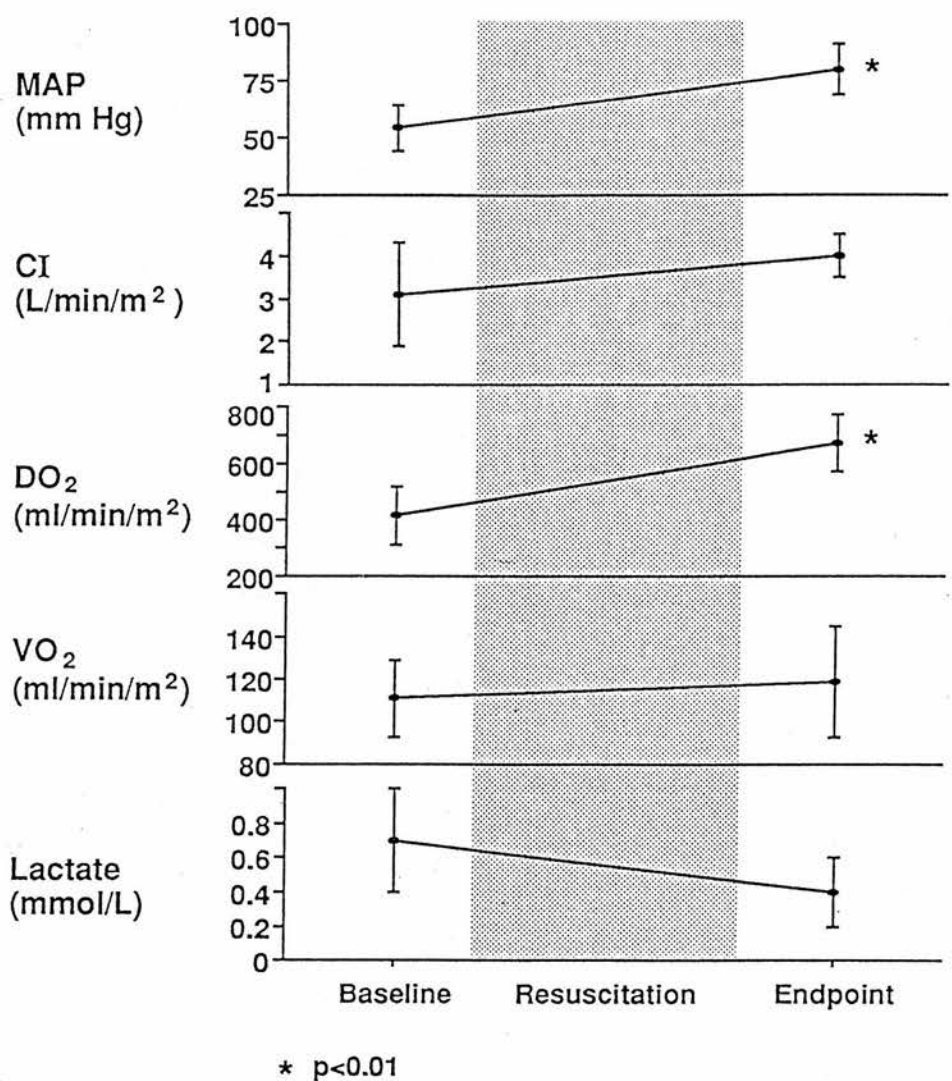


Figure 7

50% mortality compared to 100% in patients in whom lactate remained high. This group subsequently went on to demonstrate an inverse relationship between VO_2 and initial blood lactate concentrations in a comparable patient group (Duff 1969). We have confirmed that hyperlactataemia can be reversed with improvement in MAP and CI. Motsay and colleagues (Motsay 1970) also demonstrated falls in lactate concentrations as VO_2 increased in some individual cases of septic shock. Nishijima has suggested that there are significant differences in lactate between survivors and non-survivors and that survivors of septic shock had a higher cardiac index than non-survivors (Nishijima 1973). In contrast, Blair (Blair 1971) showed no correlation between initial lactate concentration and cardiac output in 30 septic shock patients, and non-survivors' had a higher cardiac index. Interpretation of the blood pressure and vascular resistance data from this paper is complicated by the prior administration of vasoconstrictor drugs in most patients.

In all of the studies cited above the aim of resuscitation was to increase blood pressure, with no attempt to maintain or increase cardiac output, and thus DO_2 . The differing results in these and contemporary studies (Vincent 1981, Vincent 1990 ii) may therefore be a reflection of the unpredictable cardiac output and oxygen transport responses to fluid administration

(Shoemaker 1985, Edwards 1989 ii) and vasoactive drug infusion in shock (Talley 1969, Meadows 1988, Mackenzie 1991 i).

In the present study blood lactate concentrations and oxygen transport variables were measured as soon as invasive monitoring was established on admission to ICU. None of the patients had received exogenous catecholamines. We documented the simultaneous responses of ABL and oxygen transport variables during resuscitation using a previously agreed therapeutic protocol constructed to aim for increases in cardiac output and DO_2 whilst concurrently reversing hypotension.

A number of retrospective studies documenting the relationship of cardiorespiratory variables and ABL have been published (Groeneveld 1987, Rashkin 1985).

Groeneveld and colleagues studied 50 patients with circulatory shock, measuring cardiorespiratory and metabolic variables before and during resuscitation. They demonstrated falls in ABL in patients with non-septic causes for shock, but not in those with septic shock. In the light of our finding that lactate falls with concurrent increases in DO_2 and reversal of hypotension it may be important to note that the mean post-resuscitation MAP in their study was 67 mmHg. The importance of reversal of hypotension was demonstrated in the landmark study of Maclean and colleagues (Maclean 1967). They showed that lactate

concentrations only fell in the groups where flow and pressure were improved together, and that isolated increases in flow did not reverse hyperlactataemia. Indeed, it is now accepted that in hyperdynamic sepsis with a high cardiac output and a very low systemic vascular resistance the use of appropriately monitored vasoconstriction, following correction of hypoxaemia and hypovolaemia, to reverse profound hypotension is often beneficial in terms of the metabolic state and renal function (Desjars 1987, Redl-Wenzl 1993). This is usually the case even when there is a limited reflex fall in cardiac output, so long as the cardiac output remains higher than normal when perfusion pressure is increased. However, the potentially catastrophic effects of vasoconstriction on tissue oxygen supply is one of the cardinal reasons why vasoconstrictor therapy should be monitored by measurement of flow-related variables, and not just by blood pressure measurement.

As previously detailed, the prognostic significance of hyperlactataemia in groups of patients in shock is repeatedly cited. Vincent's group (Vincent 1983) and Cowan and colleagues (Cowan 1984) measured serial lactate concentrations during resuscitation from shock using oxygen, mechanical ventilation, fluids and vasoactive drugs. The conclusion of both groups was that changes in lactate concentration provided an early and objective evaluation of response to therapy and ultimate prognosis. In both studies, failure of lactate

concentrations to fall was associated with poor outcome. More recently, Vincent's group have compared the prognostic value of ABL compared to oxygen transport variables during resuscitation from septic shock (Bakker 1991). They failed to show any difference in haemodynamics or oxygen transport between survivors or non-survivors, either before or after resuscitation. They did show that non-survivors had significantly higher ABL at all stages compared to survivors. The haemodynamic and oxygen transport findings of this study are in direct contradiction to the work of Tuchschiidt (Tuchschiidt 1992). In their prospective, randomised study comparing normal and supra-normal DO_2 in septic shock patients, there was a significant fall in mortality with higher DO_2 .

Other groups have studied the relationship between oxygen transport variables and ABL (Astiz 1988). In 50 patients with sepsis and 50 with myocardial infarction, the majority of whom were not in shock, they measured a full cardiorespiratory profile and ABL on admission to the intensive care unit. In neither group could they define particular values of SvO_2 , DO_2 or VO_2 which protected against hyperlactataemia. The major shortcomings of this study are its adynamic nature, in clinical conditions which are continually altering, and the assumption that all patients in a particular group are at the same stage in the pathophysiological evolution of the disease state. Careful scrutiny of the

patient groups, particularly the septic group, reveals different patterns of oxygen transport and haemodynamics to those detailed in many other studies (Maclean 1967, Shoemaker 1983, Edwards 1989). In particular, the levels of CI and SvO₂ are lower than those commonly found in sepsis. These observations indicate that the conclusions must be viewed with caution.

Rashkin (Rashkin 1985) retrospectively studied isolated measurements of lactate in a heterogeneous group of patients, mainly with respiratory failure, of whom a few were in clinical shock. In 24 of the 44 patients, oxygen transport variables were also recorded. Patients with mild to moderate liver failure were included. There was a statistically demonstrable threshold DO₂ value of 8 ml/kg/ min, below which hyperlactataemia appeared. On the basis of this small, retrospective case review the authors proposed that this DO₂ could be the optimal value to aim for in critical illness. Its applicability and relevance in general ICU is questionable.

In our present study of a heterogeneous group of 40 shock patients no particular value of oxygen transport which protects against hyperlactataemia could be identified agreeing with the findings of Astiz (Astiz 1988). However our results do suggest that the adequate DO₂ level in the individual can be determined by sequential measurements of oxygen transport variables and ABL during therapy. A confounding factor in our study is the clinical heterogeneity of the patients, and

the use of different end-points for resuscitation in low flow and high flow shock.

The effects of volume loading, blood transfusion and catecholamines on oxygen transport and lactate have previously been studied in patients with sepsis or ARDS (Haupt 1985, Gilbert 1986). These studies were performed after initial resuscitation and using fixed volumes of fluid or limited drug dosages titrated against blood pressure, perhaps limiting their clinical relevance in shock.

Two studies from Watson's group have attempted to further investigate the relationship between the metabolic and cardiorespiratory parameters during resuscitation (Hayes 1993, Hayes 1994). The two patient groups are similar and they will be considered together. The aim of the studies was to evaluate the responses to therapy aimed at achieving high CI and DO_2 , and comprising fluids, dobutamine and noradrenaline. The patients included a large number of post-operative cases and a mixture of other pathologies including ARDS and sepsis. Not all of the patients required ventilation, all received dopamine at $2\mu\text{g/kg/min}$ and no specific details of analgesia, sedation or neuromuscular blockade are provided. In the latter study there is no documentation of blood pressure.

Two groups of patients were identified in both studies. In the first, retrospective study (Hayes 1993) they confirmed the findings of Shoemaker (Shoemaker 1988) and

Boyd (1993), showing the prognostic benefit of the achievement of increased DO_2 and VO_2 concurrent with adequate MAP. The mean initial MAP was 84 mmHg in one group, and 73 mmHg in the other. The second study was randomised prospectively and the authors concluded that aggressive attempts to increase VO_2 may have been detrimental. It is possible that the very large doses of dobutamine used (up to 200 $\mu\text{g/kg/min}$), whilst not resulting in adequate CI did vasodilate, necessitating the high doses of noradrenaline used. This combination could well have worsened the tissue oxygen supply/demand balance. Rather than struggling to elevate cardiac output in these patients, it may be safer and more logical to attempt to increase nutrient tissue blood flow by fluid manipulation or with other vasoactive agents. Well conducted research is urgently required in this area.

In the light of the work summarised above, it is of interest to examine the findings in each of our patient groups in more detail.

In Group I significant increases in CI and DO_2 were not associated with overall increases in VO_2 , probably reflecting the heterogeneous nature of the patient population. It has been shown that significant increases in DO_2 in cardiogenic shock are associated with substantially increased SvO_2 and reduced OER, but with much less significant increases in VO_2 (Creamer 1990). In keeping with these findings, in our study there were

consistent increases in SvO_2 and reductions in OER reflecting increased oxygen availability with improvement of tissue hypoxia as evidenced by the falls in lactate concentrations. It could be argued that resuscitation had resulted in improved splanchnic and liver perfusion, leading to increased lactate clearance. This is a likely component of the resolution of hyperlactataemia, and further study would be of interest.

In Group II no significant increases in CI or DO_2 could be achieved, and SvO_2 and OER remained unchanged with persisting hyperlactataemia despite an increase in MAP. In these patients vigorous resuscitation failed to reverse tissue hypoxia, as indicated by unchanging levels of SvO_2 and OER. In 6 of these patients MAP was increased to over 85 mmHg, but there was no simultaneous increase in CI and DO_2 and all 6 patients died.

It has been generally accepted that an elevated blood lactate concentration is an essential inclusion in the definition of shock (Shubin 1976, Rackow 1986). The patients in Group III had profound hypotension (mean MAP 54 mmHg) along with clinical signs of shock such as oliguria and altered conscious level, and inadequate CI and DO_2 with elevated OER and reduced SvO_2 . However, ABL concentrations were within the normal range and all of these patients survived.

In our study no patient was identified in whom the ABL concentration rose when treatment led to concurrent

improvement in both haemodynamics and oxygen transport variables. We found no evidence of a lactate wash-out phenomenon. However, repeated sampling at short time intervals, perhaps every 10 or 15 minutes, would be necessary to exclude the possibility that if such a phenomenon occurs it may be early, and transient. It is possible that even if lactate is washed out of reperfused tissues, the improved hepatic perfusion and function which accompanies successful resuscitation would result in an increase in clearance of lactate, thus preventing a rise in ABL concentration.

In conclusion, we have defined three patterns of response of lactate and cardiorespiratory variables during the resuscitation of shock.

If resuscitation leads to reversal of hypotension and improved DO_2 hyperlactataemia resolves. The patients in whom blood pressure or flow could be improved individually but not concurrently had persisting or increasing hyperlactataemia. These findings highlight the need to measure and manipulate CI and DO_2 simultaneously with blood pressure. This approach has been further emphasised (Grootendorst 1990).

It appears that patients may have clinical and objective physiological evidence of shock without elevation of blood lactate concentrations. This reflects the complex processes which affect ABL, and the realisation that both the hypoxic threshold and lactate clearance mechanisms must be grossly exceeded before

hyperlactataemia supervenes.

4.1. Introduction

In Chapter 3 the findings of a study relating oxygen transport to blood lactate concentration in a heterogeneous group of patients with shock are detailed. The lack of a relationship between increases in DO_2 and hyperlactataemia could reflect the mixture of low and high flow shock, and the accompanying abnormalities of vasoregulation in the septic patients. A number of investigators have stated that pathological supply dependency of VO_2 on DO_2 is predicted by hyperlactataemia in sepsis and ARDS. In this study we examine this relationship.

Hyperlactataemia is known to be a consequence of tissue hypoxia (Huckabee 1958, Weil 1970). There are, however, many causes of hyperlactataemia other than tissue hypoxia and these include hyperglycaemia, hypocapnia, toxins and liver dysfunction (Figure 1; Huckabee 1958, Cohen and Woods 1976). The clinical classification of lactic acidosis proposed by Cohen and Woods (Cohen and Woods 1976) attempted to separate those patients with tissue hypoxia from those without. The clinical distinction between the groups was on the basis of the simple clinical parameters of pulse, cuff blood pressure, the presence or absence of cyanosis, skin turgor, skin temperature in the extremities and urine

output. The cases which were used to separate the two classes, Type A (shock) and Type B (no shock), were collected retrospectively from a number of publications between 1961 and 1975. A major problem with this data is highlighted by the authors themselves when discussing blood pressure, skin turgor and colour, and peripheral perfusion:

"we have again arbitrarily accepted that no gross abnormalities were present unless specifically noted by the authors". In a number of these patients blood pressure was not documented at all. However, these points and the arbitrary threshold for hypotension as cuff systolic BP of $< 100\text{mmHg}$ are less relevant in the light of current knowledge. It is now apparent that tissue hypoxia may be present without the clinical criteria of shock which are detailed (Arieff 1992). Even using sophisticated invasive monitoring it can be difficult to assess the adequacy of oxygen transport. The cardiorespiratory findings in septic shock and ARDS, especially after volume resuscitation, may include increased cardiac output and normal or increased oxygen delivery.

Despite the presence of an apparently adequate DO_2 there is an impediment to normal tissue oxygen utilisation which has long been recognised but is still not fully understood (Duff 1969, Danek 1980)). Whatever the mechanisms increases in VO_2 can often be achieved by increasing DO_2 using fluids, blood or vasoactive drugs,

even when DO_2 is considerably higher than the normal levels at which delivery dependence has been shown to occur (Mohsenifar 1984, Clarke 1991). This delivery dependent oxygen consumption is a pathological state which is in stark contrast to the norm where VO_2 is independent of DO_2 above a critically low level of 330 ml/min/m² (Shibutani 1983). Subsequent work has suggested that elevated ABL concentrations characterise those patients with shock or ARDS who exhibit delivery dependent VO_2 (Vincent 1990 i, Kruse 1990). However, as detailed in Chapter 3, hyperlactataemia is not a universal finding in shock.

In this study the association between ABL concentrations and the DO_2/VO_2 response to resuscitation was examined to determine whether hyperlactataemia predicted delivery dependence.

4.2. Patients and methods

4.2.1. Patients

Twenty three patients (mean age 55, range 33-81) requiring intensive care, invasive haemodynamic monitoring and mechanical ventilation for the management of septic shock (n=21) and ARDS (n=23) were studied. Septic shock was defined as MAP <70 mmHg with oliguria despite controlled volume expansion to an optimal pulmonary artery occlusion pressure, in the presence of positive bacteriology.

ARDS was defined as severe hypoxaemia requiring ventilation with FiO_2 >50% to maintain PaO_2 >10 kPa;

diffuse infiltrates on CXR ; $Q_s/Q_t > 30\%$; PAOP < 18 mm Hg; in the presence of reduced compliance and a known risk factor (Table 1).

4.2.2. Protocol

All patients were sedated with continuous infusions of an opioid (papaveretum 3-5mg/hr) and a benzodiazepine (midazolam 1-3 mg/hr) and paralysed with atracurium. No changes in rates of infusion were made during the study period, and the only adjustments to ventilator settings were of FiO_2 . All patients were studied during the first six hours of resuscitation following admission to ITU. All patients had femoral arterial and thermodilution pulmonary artery flotation catheters, and cardiorespiratory measurements and ABL measurements were made as described in Chapter 2.

4.2.3. Resuscitation

Following baseline measurements, controlled volume expansion was performed in all patients after comparison of the haemodynamic profile with previously described therapeutic goals: MAP > 80 mmHg, CI > 4.5 l/min/m² and $DO_2 > 600$ ml/min/m² (Shoemaker 1973). Combinations of colloid and blood were used depending on haemoglobin level. Once volume expanded, all patients received suitable combinations of vasoactive drugs depending on the haemodynamic profile, and these were then titrated against the observed haemodynamic effects aiming for the defined therapeutic

goals. The baseline variables were compared to the variables associated with maximal DO_2 within the first six hours of resuscitation. Patients were divided into two groups on the basis of initial ABL concentrations. Group 1 had ABL concentration $<2 \text{ mmol/l}$, and Group 2 had ABL concentration $>2 \text{ mmol/l}$. This threshold for significant hyperlactataemia is that previously described by Vincent and colleagues (Vincent 1990 i) in the same patient population.

4.2.4. Statistical analysis

All results are expressed as mean \pm SEM. Baseline data from the two groups of patients were compared by means of the Wilcoxon rank sum test, and the paired data obtained before and after resuscitation were compared with the Wilcoxon signed rank test. Differences were considered significant at $p < 0.05$.

4.3. Results

The 23 patients (11 female) were each studied on one occasion. Clinical data including Apache II scores are shown in Table 6, and haemodynamic and oxygen transport data in Tables 7 and 8. Baseline measurements were compared in the two groups. Group 2 had significantly higher heart rate and DO_2 with lower blood pressure. Lactate concentrations were significantly higher in Group 2.

Following resuscitation there were significant comparable increases in CI, SvO_2 and DO_2 , and falls in

Table 6.

Clinical details : Group 1.

Patient	Age	Sex	Primary diagnosis	Apache II	Vasoactive drug (ug/kg/min)	Outcome
1	58	F	Pneumonia Beta-haemolytic streptococcal SS	27	NOR 0.05 DOP 3 DOB 15	S
2	63	F	Pneumonia Cardiorespiratory arrest SS	15	DOB 10	S
3	68	M	Faecal peritonitis ARDS	22	DOB 3	S
4	38	F	Guillain Barre SS, ARDS	12	NOR 0.05 ADR 0.06	NS
5	73	M	Acute pancreatitis Perforated colon SS, ARDS	21	DOB 30 NOR 0.4	NS
6	54	F	Pneumococcal pneumonia SS, ARDS	10	NOR 0.07	NS
7	72	M	SS	28	DOB 15 NOR 0.28	NS
8	57	M	Perforated diverticulum ARDS	3	DOB 5	S
9	80	M	Subphrenic collection post gastrectomy, SS, ARDS	25	DOB 4 NOR 0.12	NS
10	52	F	Pneumococcal pneumonia ARDS	21	DOP 2 NOR 0.08	S
11	65	F	SS, ARDS	21	DOB 5	NS
12	64	F	SS (enterococci), ARF	25	DOB 15	NS
13	45	M	Necrotising fasciitis, SS, ARDS	16	NOR 0.05	S

Clinical details : Group 2.

14	81	F	Faecal peritonitis Respiratory arrest, SS	18	ADR 0.04	NS
15	59	F	Empyema, SS (beta-haemolytic streptococci) Squamous carcinoma of lung	27	DOB 5 ADR 0.06	NS
16	63	M	SS (beta-haemolytic streptococci) Pneumonia Respiratory arrest	25	DOB 10 NOR 0.03	NS
17	65	F	Necrotising fasciitis SS	20	DOB 12	S
18	73	M	SS (coliforms) Indwelling urinary catheter	31	ADR 0.4 NOR 0.9	NS
19	75	M	Faecal peritonitis Infarcted colon, SS	18	NOR 0.14	NS
20	58	M	Ulcerative colitis Infarcted small bowel	21	NOR 2	NS
21	80	M	Pneumonia SS	33	NOR 0.04 ADR 0.06	NS
22	42	F	Post colectomy SS	15	DOB 5 NOR 0.3	S
23	70	M	Post cystectomy (carcinoma bladder) SS	35	ADR 0.15 NOR 0.2	S

SS, septic shock; ARDS, adult respiratory distress syndrome; ARF, acute renal failure; DOP, dopamine; DOB, dobutamine; ADR, adrenaline; NOR, noradrenaline; S, survivor; NS, nonsurvivor.

Table 7.

Haemodynamic variables at baseline and after initial resuscitation

	Group 1 (Lactate < 2 mmol/l) n = 13		Group 2 (Lactate > 2 mmol/l) n = 10	
	Baseline	Resus	Baseline	Resus
HR (beat/min)	109 (6)	117 (5)	128 (5)**	127 (4)
MAP (mmHg)	70 (3)	78 (4)*	63 (2)	69 (5)
PAOP (mmHg)	13 (2)	15 (1)	13 (2)	13 (1)
CI (l/min/m ²)	3.7 (0.4)	5.0 (0.2)*	3.9 (0.4)	4.9 (0.3)*

Difference from baseline : * p < 0.05;

Between group comparison : ** p < 0.05.

Table 8.

Lactate and oxygen transport variables at baseline and after initial resuscitation.

	Group 1 (Lactate < 2 mmol/l) n = 13		Group 2 (Lactate > 2 mmol/l) n = 10	
	Baseline	Resus	Baseline	Resus
DO ₂ (ml/min/m ²)	484 (36)	730 (44)**	549 (54) ⁺	779 (54)*
VO ₂ (ml/min/m ²)	137 (7)	147 (6)	145 (12)	133 (6)
OER (%)	29 (2)	21 (1)*	28 (3)	18 (2)*
SvO ₂ (%)	69 (2)	77 (1)*	71 (3)	80 (2)*
Qs/Qt (%)	28 (3)	32 (3)	27 (3)	34 (3)
Lactate (mmol/l)	1.2 (0.1)	1.1 (0.1)	3.7 (0.4) ⁺	3.7 (0.4)

Difference from baseline : *p < 0.05, **p < 0.005;
between group comparison : ⁺p < 0.05

oxygen extraction in both groups. In both groups resuscitation with colloid, blood and vasoactive drugs resulted in significant increases in DO_2 : Group 1 from 484 ± 36 to 730 ± 44 ml/min/m² $p < 0.005$; Group 2 from 550 ± 54 to 780 ± 54 ml/min/m² $p < 0.05$ but in neither group was there a significant change in VO_2 .

These pooled data obscure the finding that in both groups there were individual patients who exhibited VO_2 delivery dependency. Only in Group 1 was there a significant increase in MAP ($p < 0.05$). There were no significant changes in VO_2 or ABL concentration in either group, although there were marked individual changes in VO_2 in some patients in each group. Pooled data for Groups 1 and 2 are represented diagrammatically in Figures 8 and 9 respectively, with the individual patient DO_2/VO_2 responses in Figures 10 and 11.

4.4. Discussion

It has been recognised for many years that inefficient utilisation of oxygen is a fundamental defect in septic shock (Duff 1969). This finding has been confirmed recently and a similar situation has been described in ARDS (Edwards 1989 i, Clarke 1991). The pathophysiological abnormality is characterised by dependence of VO_2 on delivery at levels of DO_2 which are well above the previously described critical level (Shibutani 1983). Oxygen consumption can

Group 1 Lactate < 2 mmol/l (n=13)

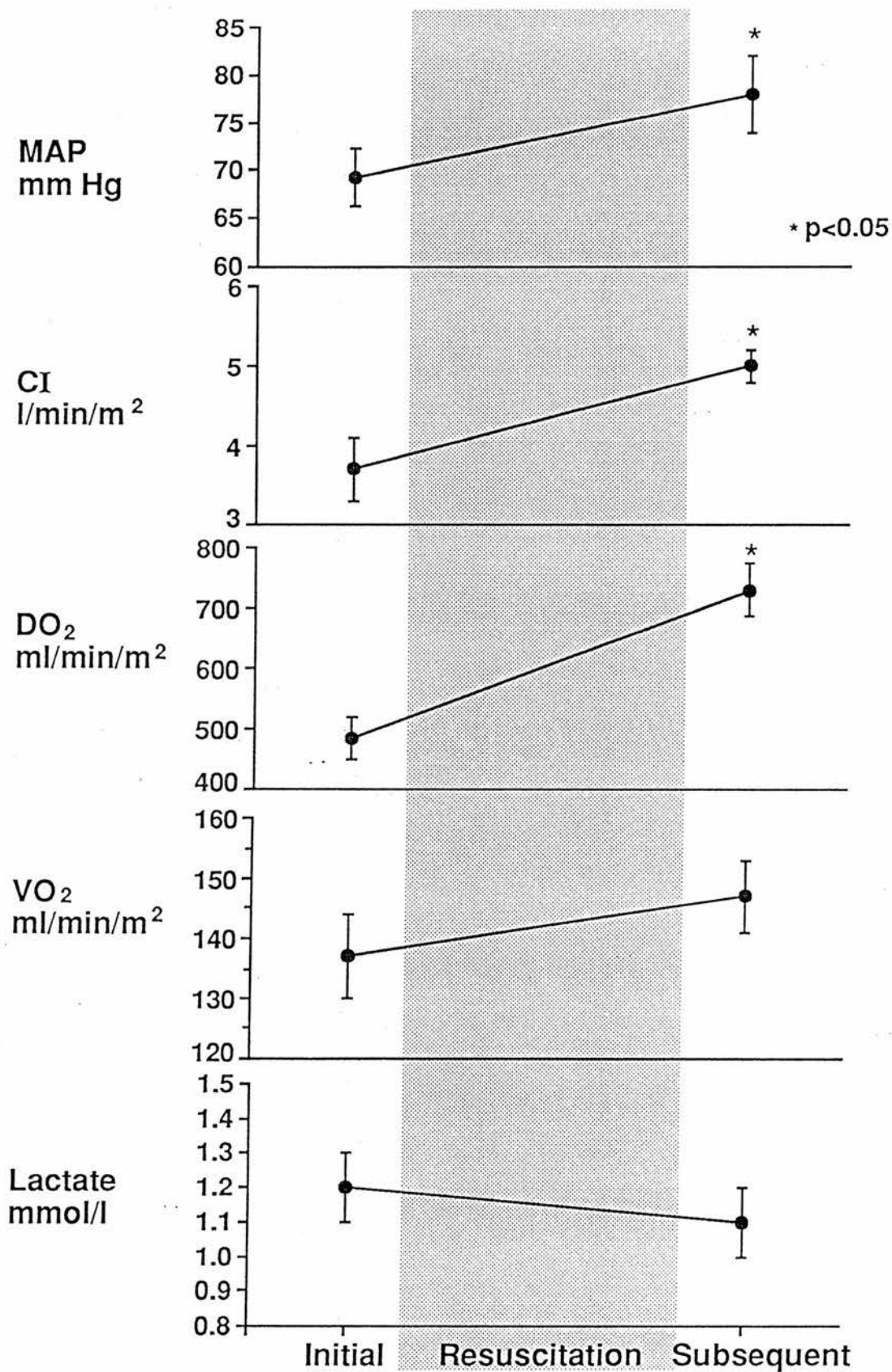


Figure 8

Group 2 Lactate > 2 mmol/l (n=10)

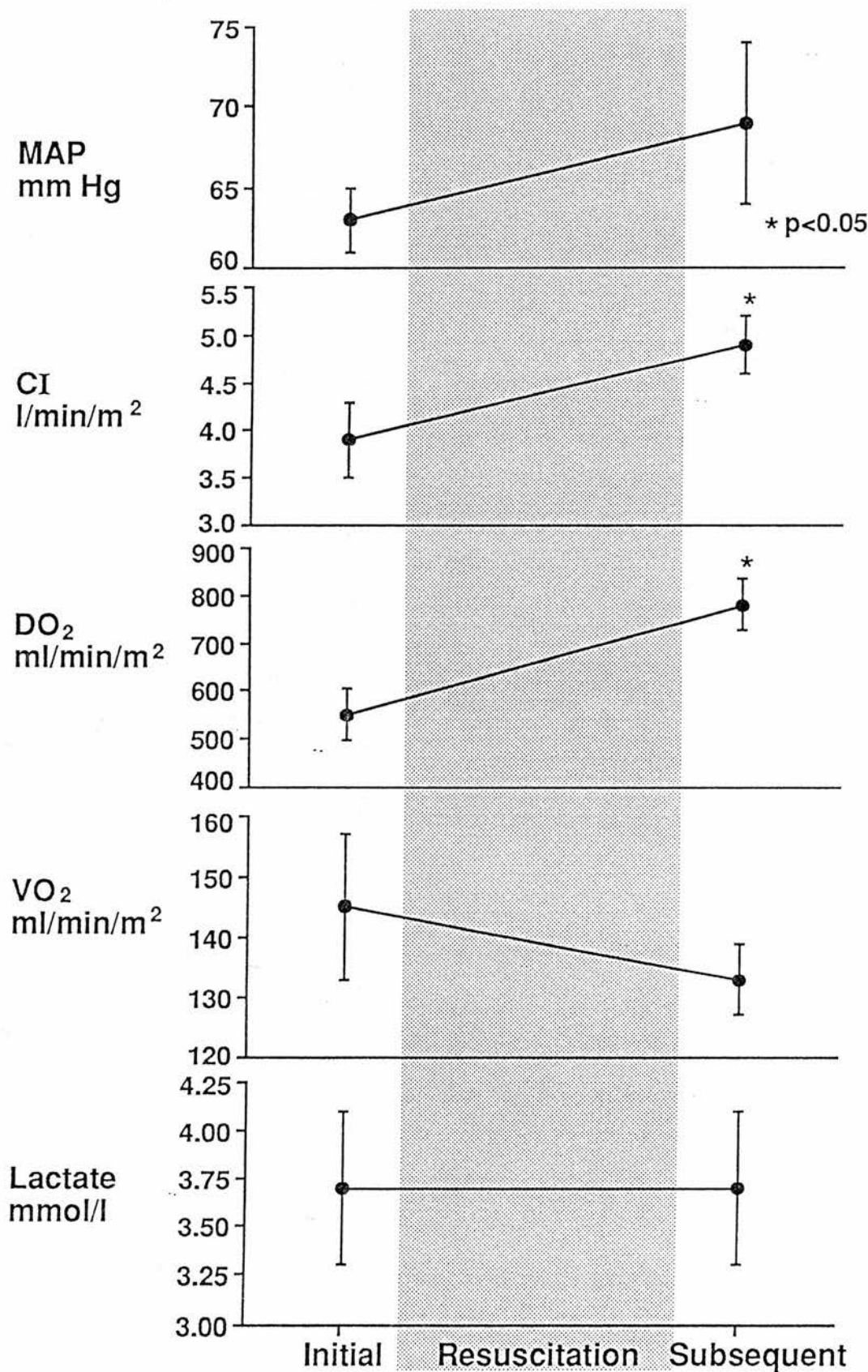


Figure 9

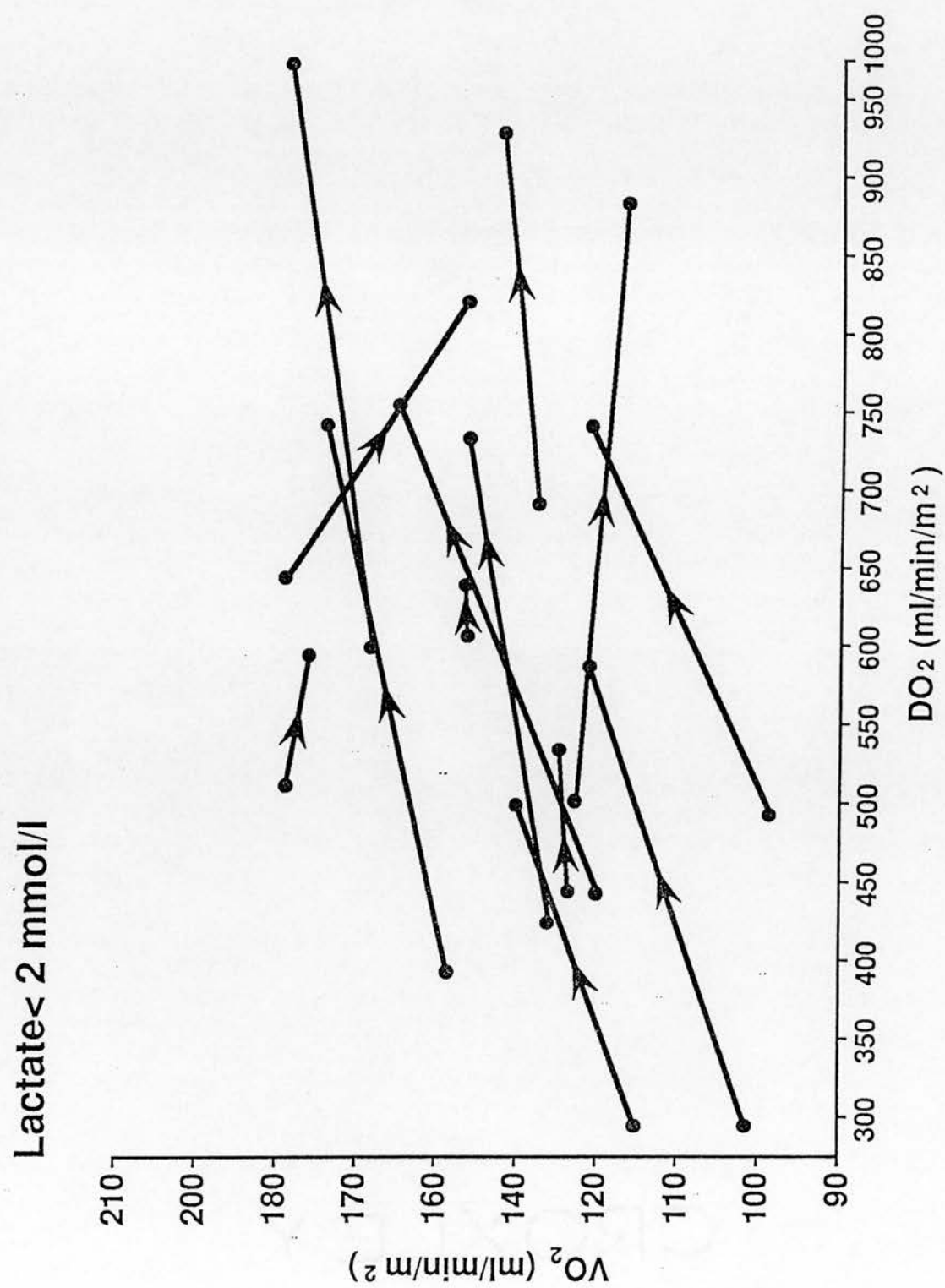
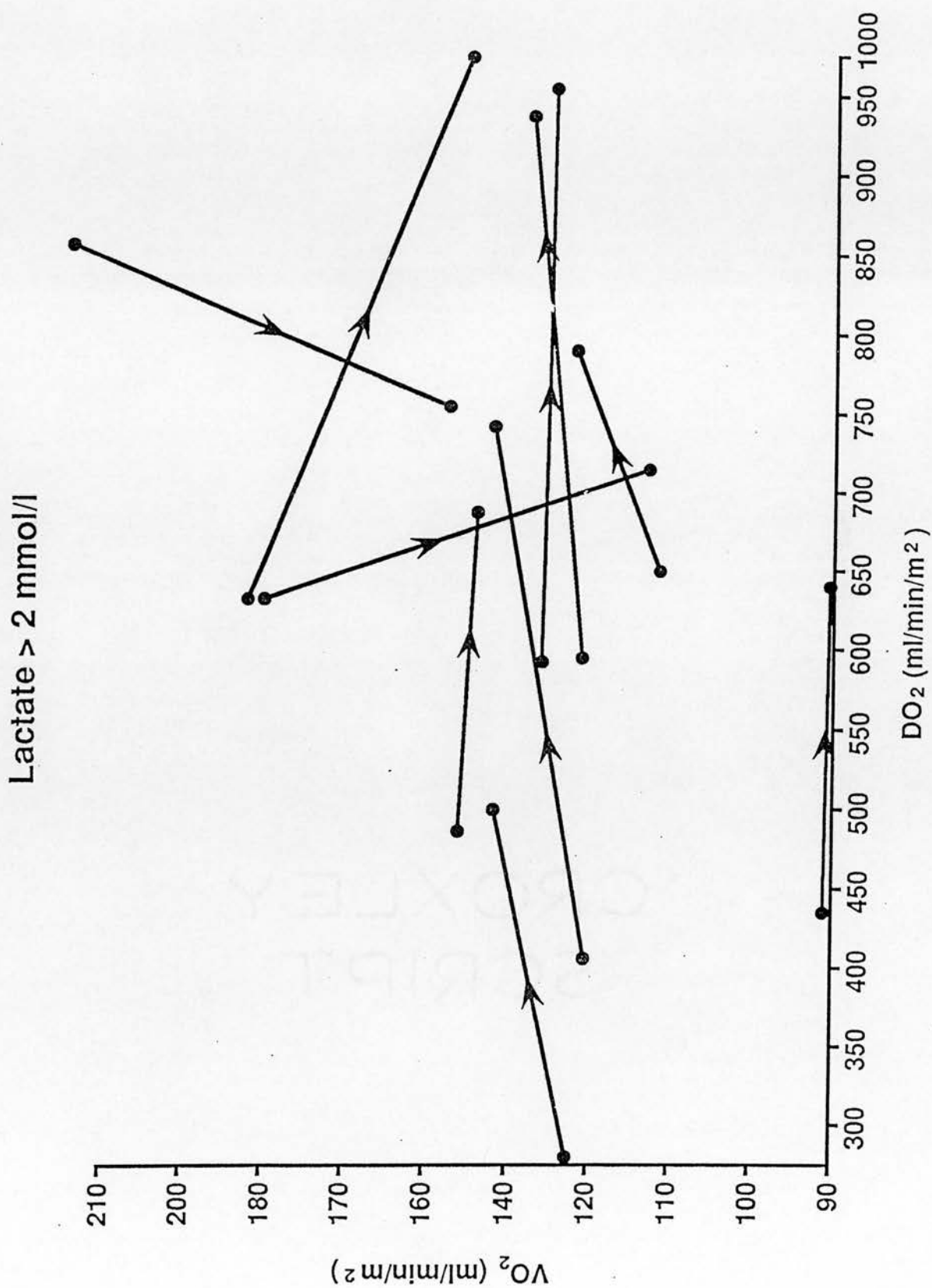


Figure 10



thus be increased by increasing delivery, suggesting that tissue perfusion is inadequate.

The mechanisms of this phenomenon are not completely clear but probably involve a combination of factors including :

1. Maldistribution of tissue blood flow due to vasoderegulation (Abraham 1983). Passage of excess blood through areas of low metabolic activity results in a fall in oxygen extraction ratio, while relative lack of blood flow through areas of high metabolic activity may result in delivery dependence. The balance of these factors will determine the response to resuscitation.
2. An increase in capillary to cell diffusion distance caused by the interstitial oedema associated with capillary leak (Ellman 1984).
3. Dysfunction of organelles as a result of the mediators and toxic elements generated and released in the inflammatory response to sepsis and ARDS (Schumer 1983).

In addition the balance of oxygen supply and demand may be adversely affected by the increased tissue oxygen requirements generated by fever, shivering or rigors (Skootsky 1988).

It has been suggested that it is only in those individuals with severe tissue hypoxia and critically elevated ABL concentrations that $\dot{V}O_2$ rises significantly in response to increases in $\dot{D}O_2$. This is in accordance with the study of Duff (Duff 1969) who showed that

septic patients with the highest ABL concentrations had the lowest VO_2 levels. There is, however, some disagreement about the value of hyperlactataemia as a predictor of supply dependency in sepsis and ARDS.

Vincent and colleagues have used low dose dobutamine (5 $\mu\text{g/kg/min}$) to perform a short oxygen flux test in an attempt to disclose supply dependency of VO_2 in stable patients with heart failure or sepsis (Vincent 1990 i). Dobutamine resulted in significant increases in CI and DO_2 , but VO_2 increased only in those patients with elevated ABL concentrations.

Gilbert and colleagues also demonstrated increased VO_2 with increased DO_2 in response to infused catecholamines in septic patients with hyperlactataemia (Gilbert 1986). Further evidence for "occult" tissue hypoxia comes from the work of Bihari and co-workers (Bihari 1987). These investigators examined the hypothesis that inadequate tissue oxygenation may occur in critically ill patients despite the presence of an apparently adequate systemic blood flow, blood pressure and arterial oxygen tension. Twenty seven patients requiring assisted ventilation for respiratory failure were studied, 22 fulfilling criteria for ARDS. Full cardiorespiratory profiles were obtained at baseline, and then a low-dose prostacyclin infusion was given with repeat measurements at 30 minute intervals throughout. The infusion resulted in significant falls in blood pressure and PaO_2 in survivors and non-survivors.

Mean baseline DO_2 was 420 ml/min/m^2 in survivors, and 375 ml/min/m^2 in non-survivors. Prostacyclin resulted in increases in these variables to 552 ml/min/m^2 and 408 ml/min/m^2 respectively. There was a significant rise in VO_2 in the non-survivors (132 ml/min/m^2 to 164 ml/min/m^2) but not in the survivors. No details of ABL concentrations were presented although this study has been quoted as further evidence of the predictive value of hyperlactataemia for pathological supply dependency (Mizock 1989, Arieff 1992). There are a number of features of this study which limit its usefulness. Systemic hypotension was defined as $\text{MAP} < 45 \text{ mmHg}$, and hypovolaemia as $\text{PAOP} < 6 \text{ mmHg}$, both much lower than most investigators would accept. Additionally, the baseline levels of oxygen transport and cardiac index for a group of patients predominantly with volume and catecholamine (dopamine $3\text{--}12 \text{ ug/kg/min}$) resuscitated ARDS are lower than has been suggested is optimal (Shoemaker 1988). In the light of these observations, and the fact that the non-survivors had a metabolic acidosis throughout as evidenced by mean base deficit levels (-6 mmol/l), it could be suggested that the study did not detect occult tissue hypoxia, but simply unmasked significant, primary under-resuscitation. The ABL concentrations which are not available in this study would be of great interest. Our previous work has suggested that the relationship between tissue hypoxia and hyperlactataemia in shock is much less clear cut than has previously been suggested

(Chapter 3).

There is a subgroup of patients with the clinical and haemodynamic features of shock who have normal ABL concentrations.

Since the presence of subclinical tissue hypoxia is likely to be integral to the development of multiple organ failure, in the light of the conflicting evidence and the possibility that unrecognised tissue hypoxia may be present even in the absence of a critically elevated ABL this study was performed to assess the usefulness of initial ABL concentrations as a guide to those patients with pathological delivery dependence of VO_2 . We chose to include unstable patients during initial resuscitation in contrast to most of the investigations mentioned above, in which relatively stable, resuscitated patients were studied. We were particularly interested in the DO_2/VO_2 response in patients without hyperlactataemia over this initial period.

The timespan of study was similar to that of previous work (Broder 1964, Kruse 1990). It might be suggested that overall oxygen demand could change substantially over the study period described. This is a valid point, although work with continuous SvO_2 monitoring and continuous on-line VO_2 measurement shows that oxygen demand can change significantly from minute to minute in otherwise apparently stable patients (Nelson 1987, Skootsky 1988).

Unlike many other investigators we have carefully

documented other factors which may affect VO_2 or lactate independently. Patients with hyperglycaemia and liver failure were excluded, and all patients were sedated and mechanically ventilated. The contribution of work of breathing to VO_2 and lactate production has been shown clinically and experimentally to be considerable (Aubier 1982).

We divided our patients on the basis of ABL concentration rather than the type of resuscitation therapy received. Previous studies have concentrated on the use of either volume or vasoactive drugs. The DO_2/VO_2 /lactate relationships of our patients to the combination of volume loading with colloid and blood, and the subsequent addition of vasoactive drugs was assessed. In both groups significant increases of CI and DO_2 were achieved, but in the hyperlactataemic patients the rise in blood pressure achieved was not significant despite the vigorous administration of fluids and vasopressors. As documented in Chapter 3 it appears that hyperlactataemia will be reliably cleared in shock patients only when flow, DO_2 and blood pressure are increased concurrently. This hypothesis is supported by the results of those studies where CI and DO_2 have been increased with no accompanying improvement in MAP from low levels (MacLean 1967). In patients remaining hypotensive despite significantly increased blood flow, ABL concentrations remained high or rose further with 100% mortality.

The controversies surrounding the DO_2/VO_2 relationship in SS are as marked as those in ARDS. Silverman has demonstrated that changes in VO_2 with increased DO_2 are independent of ABL concentrations, and suggests that optimal levels of VO_2 are variable, and that serial lactate determinations should be used to assess adequacy of resuscitation (Silverman 1991). Bakker and co-workers have compared oxygen transport variables and ABL concentrations in 48 patients with SS, and have shown that DO_2 and VO_2 are poor predictors of mortality, but that ABL concentrations, particularly trends, are good prognostic indicators (Bakker 1991). From this they conclude that lactate measurement alone can serve as a reliable guide to therapy. We and other investigators have not found this to be the case. A prospective randomised study of therapy aiming for supranormal DO_2 versus conventional goals in SS documented a reduction in mortality and organ failure in the group with DO_2 increased to supranormal values by therapy appears to emphasise the importance of achieving high levels of CI and DO_2 (with concurrent reversal of hypotension) in this condition (Tuchschmidt 1992). In addition the study of Boyd and colleagues repeating the earlier studies of Shoemaker in high risk surgical patients, and confirming the ability to reduce morbidity and mortality by appropriate cardiorespiratory manipulation, provides further persuasive evidence of the importance of oxygen transport measurement and manipulation (Boyd 1993).

In their study of 20 patients with severe ARDS, Clarke and colleagues showed that supply dependency persisted despite levels of DO_2 up to 1550 ml/min/m^2 (Clarke 1991). They also failed to demonstrate a plateau in the DO_2/VO_2 relationship, a phenomenon which continues to be described using 'pooled' group data. Russell and colleagues investigated the DO_2/VO_2 relationship using indirect calorimetry to measure VO_2 , and thermodilution to measure DO_2 (Ronco 1991). Interestingly, they showed no delivery dependency, even in those patients with significant hyperlactataemia. They suggested that mathematical coupling of DO_2 and VO_2 could explain the findings of previous studies. It is notable that an earlier study from the same workers showed both pathological delivery dependence, and the ability of hyperlactataemia to predict it (Fenwick 1990). The results of our study suggest that ABL concentrations fail to predict delivery dependent oxygen consumption, but in contrast to Russell's findings, there are increases in VO_2 with increased DO_2 in patients with either normal or elevated lactate concentrations. The interpretation that this suggests the presence of covert tissue hypoxia despite normal ABL concurs with the work of Dantzker (Dantzker 1991).

In our study the inability to improve flow and MAP together in 6 patients was associated with increasing ABL concentrations and death. The influence of the underlying disease process, the inability to eradicate

sepsis and preexisting severe cardiorespiratory dysfunction on the response to therapy have all been suggested as potential reasons for the poor outlook of these patients.

Examination of the DO_2/VO_2 relationships of individual patients reveals another fascinating discrepancy. The pooling of data for statistical analysis obscures individual idiosyncratic responses of VO_2 to DO_2 . In particular, VO_2 increased by between 17 and 35% in 6 patients with normal lactate levels. There were no increases in lactate and this suggests that the increase in VO_2 was not demand led by a catecholamine induced rise in metabolism. It is possible that unrecognised tissue hypoxia is present in critically ill patients even in the absence of critically elevated ABL concentrations. As the production of hyperlactataemia in experimental models often requires combinations of severe anaemia, hypoxia, reduced cardiac output and profound hypotension the finding of hyperlactataemia in clinical situations is likely to indicate an advanced degree of tissue hypoxia.

The finding of normal ABL concentrations in patients with acute cardiorespiratory failure due to sepsis and ARDS may not, thus, preclude the presence of a tissue oxygen debt (Nimmo 1992, Arieff 1992).

Basic therapy in these patients should therefore be directed to improving DO_2 and blood pressure concurrently whilst attempting to correct or remove the

underlying cause. The levels of DO_2 and MAP required in any individual situation remain very difficult to determine although a randomised study has shown an improvement in survival when supranormal DO_2 is achieved (Tuchschmidt 1992). This suggests that although the presence of hyperlactataemia remains a serious finding, the absence of hyperlactataemia does not preclude delivery dependence of VO_2 with the attendant potential for tissue hypoxia.

It appears clear that the finding of a normal ABL concentration should not encourage complacency.

It is probably fair to suggest that oxygen transport variables and lactate should be measured, repeatedly, together, and that no single parameter can be absolutely relied upon to guide resuscitation and correct tissue hypoxia.

5.1. Introduction

As documented in Chapters 3 and 4 maintenance of tissue oxygen delivery at a level sufficient to meet demand is pivotal to survival from critical illness. As previously described, in many clinical situations, such as septic shock (SS) and ARDS, there is a defect of tissue oxygen utilisation so that $\dot{V}O_2$ is dependent on oxygen delivery, even with levels of $\dot{D}O_2$ which are normal or supra-normal (Kariman 1985, Clarke 1991). Conversely, in low cardiac output states such as cardiogenic shock oxygen extraction is generally maintained or increased with resultant reduction in SvO_2 . In either situation the balance of oxygen delivery to consumption is critical, and may be crucially affected by changes in either oxygen delivery or tissue oxygen demand. Factors which can affect demand include sedation, muscle relaxation and mechanical ventilation.

Propofol (2,6 Di-isopropylphenol), a phenol derivative, was identified as a potentially useful intravenous anaesthetic agent in 1977, and has become widely used in general anaesthesia. It is being increasingly used as a sedative agent in the intensive care unit (Newman 1987).

Like other agents with sedative activity, it has the potential to affect the oxygen supply/demand relationship both detrimentally by decreasing cardiac output and thus DO_2 , or beneficially by reducing oxygen demand.

When used for induction and maintenance of anaesthesia, it has been shown to have a number of haemodynamic effects including substantial reductions in heart rate, cardiac output, blood pressure and systemic vascular resistance (Foex 1991). However, the precise cardiorespiratory effects of the subanaesthetic doses used for sedation in critically ill adult patients dependent on vasoactive drugs for haemodynamic stability have not been rigorously investigated.

The aim of this study was to document the effects of a sedative infusion regimen of propofol on haemodynamics, oxygen transport and blood lactate concentrations.

Futhermore, in an attempt to unravel the mechanism of any effect on VO_2 , resuscitation with fluid and/or vasoactive drugs was used after 3 hours sedation to restore MAP, cardiac output and DO_2 to baseline levels. Subsequently, any residual decrease in VO_2 could be attributed to a decrease in oxygen demand. Blood lactate concentrations were measured as a further index of the adequacy of tissue oxygenation.

5.2.

Patients and methods

Ten severely ill patients requiring mechanical ventilation and with femoral and pulmonary artery catheters in situ for standard clinical monitoring were studied. The mean age was 56 (range 38 to 80), and 5 were female.

Protocol

All patients had been initially resuscitated using combinations of colloid and blood to achieve optimal PAOP with the addition of an inotrope and/or vasopressor to achieve a stable $CI > 4 \text{ l/min/m}^2$ with $MAP > 80 \text{ mmHg}$. They had all achieved haemodynamic stability, and were on unaltered doses of vasoactive agents for at least 2 hours prior to the start of the study.

All patients received papaveretum at a fixed infusion rate for 6 hours before and throughout the study. Other sedation was discontinued several hours prior to the study, and the study began when further sedation was required. No muscle relaxants were used.

Immediately before commencement of propofol infusion a full baseline cardiorespiratory profile, as detailed in Chapter 2, was performed. Simultaneously, assessment was made of conscious level using the Ramsay sedation score (Ramsay 1974) and arterial whole blood was drawn for lactate measurement.

Following these baseline measurements, propofol was infused according to a decreasing infusion rate regimen

designed on the basis of known pharmacokinetic data to rapidly achieve and thereafter maintain a blood level of 1 ug/ml (Albenese 1990). This consisted of 4 mg/kg/hr for 10 minutes, 3mg/kg/hr for 50 minutes and then 2mg/kg/hr for the remaining 5 hours of the study. Cardiovascular measurements were repeated 10 and 30 minutes after commencement of the propofol infusion, and then all measurements (haemodynamic, oxygen transport, lactate and sedation score) were repeated at 1 hour, 3 hours and 6 hours. In 6 patients modified PACs with fast response thermistors were inserted and right ventricular ejection fraction (RVEF) and volumes were measured (REF-1, Baxter Edwards, Irvine, California). No patient had to be withdrawn from the study because of clinically important falls in MAP or cardiac output. After 3 hours of propofol sedation, cardiac output and DO_2 were restored to as near baseline as possible using a combination of colloid to restore PAOP and/or vasoactive drugs as appropriate. Statistical analysis was carried out using the Wilcoxon signed rank test to compare data at baseline and 3 hours. All values are expressed as mean \pm SEM. Variables at 6 hours were not analysed since manipulation had resulted in a restoration to initial values.

5.3. Results

The clinical details of the patients studied are shown in Table 9, and the cardiorespiratory data at the

individual study points are detailed in Table 10 . Heart rate, MAP, cardiac output and SVR are shown graphically in Figure 12, and DO_2 , VO_2 , ABL concentration and Ramsay sedation score in Figure 13.

Infusion of propofol was associated with significant reductions in HR, MAP and SVR. Stroke volume and, in the 6 patients where it was measured, RVEF were unchanged. There was no significant change in CVP and PAOP from the pooled data, but in 3 patients (nos. 2, 7 and 10) there were marked falls requiring fluid infusion to restore filling pressures and cardiac output at three hours but not before.

There was a trend towards a reduction in both CO and DO_2 at 3 hours, but neither achieved statistical significance. There was a similar trend in VO_2 . There were no significant changes in ABL concentration. As anticipated the Ramsay sedation score changed significantly from 2.65 ± 0.27 to 5.0 ± 0.29 .

The therapeutic interventions required to restore cardiac output and DO_2 are shown in Table 9, and their effects on haemodynamics and oxygen transport in Table 10 and the Figures 12 and 13.

Heart rate, MAP and DO_2 were successfully restored to baseline, DO_2 and VO_2 rising in parallel, and there were no changes in ABL concentrations or sedation level.

Table 9.
Details of Patients

No	Age	Weight	Apache II	Diagnosis	Inotrope	Therapy at 3 hrs.
1	67	80	22	Acute pancreatitis ARDS Septic shock	DOB	DOB
2	78	60	24	Oesophago- gastrectomy Septic shock ARDS	DOB	DOB PPS
3	48	80	21	G-I haemorrhage Septic shock	NOR	NOR
4	70	75	21	Acute pancreatitis Septic shock	DOB	DOB
5	70	80	23	Septic shock Post cystectomy	ADR NOR	PPS
6	81	80	29	Pneumonia Mitral valve disease	ADR DOP	DOB
7	64	70	15	Perf. duodenal ulcer Septic shock Acute renal failure	DOP	DOP PPS
8	67	45	31	Septic shock Acute renal failure	DOP	DOP
9	74	75	22	Perforated colon Septic shock ARDS	DOB DOP NOR	No change
10	76	85	23	Perf. duodenal ulcer Septic shock ARDS	DOB NOR	No change

DOB, Dobutamine; DOP, Dopamine; ADR, Adrenaline;
NOR, Noradrenaline; PPS, Plasma protein solution.

Table 10.
Cardiovascular and oxygen transport variables, whole blood lactate and sedation scores before and during propofol infusion (mean \pm SE)

	Before	30 min	60 min	3 h	6 h
HR (beats/min)	97.3 \pm /_4.0	93.6 \pm /_2.9	91.5 \pm /_3.6	85.7 \pm /_3.9*	96.0 \pm /_5.3
MAP (mmHg)	87.6 \pm /_3.7	78.4 \pm /_3.4	79.8 \pm /_3.7	76.2 \pm /_4.1*	85.2 \pm /_2.7
CVP (mmHg)	12.4 \pm /_1.5	11.1 \pm /_1.2	11.3 \pm /_1.2	11.3 \pm /_1.0	12.4 \pm /_1.2
PAOP (mmHg)	14.2 \pm /_1.5	11.5 \pm /_1.6	12.1 \pm /_1.4	12.7 \pm /_1.5	13.4 \pm /_1.5
CI (l/min/m ²)	4.44 \pm /_0.42	4.43 \pm /_0.45	4.3 \pm /_0.39	4.13 \pm /_0.36	4.36 \pm /_0.4
SVI (ml/min ²)	46.2 \pm /_4.8	48.3 \pm /_5.6	48.2 \pm /_4.6	49.2 \pm /_4.5	47.2 \pm /_5.7
LVSWI (g.m/m ²)	46.1 \pm /_5.8	43.0 \pm /_4.0	42.4 \pm /_3.9	41.1 \pm /_3.0	46.0 \pm /_5.8
RVSWI (g.m/m ²)	13.3 \pm /_2.0	11.7 \pm /_1.9	11.6 \pm /_1.6	11.6 \pm /_1.5	11.5 \pm /_2.0
RVEF (%, n=6)	38.7 \pm /_4.8	39.5 \pm /_5.9	42.0 \pm /_6.1	37.5 \pm /_4.9	33.7 \pm /_5.3
SVRI (dynes sec/cm ⁵ m ²)	1461 \pm /_137	1360 \pm /_166	1405 \pm /_180	1327 \pm /_141*	1435 \pm /_132
DO ₂ (ml/min/m ²)	660 \pm /_66		632 \pm /_58	596 \pm /_54	641 \pm /_70
VO ₂ (ml/min/m ²)	132 \pm /_9		130 \pm /_8	122 \pm /_5	130 \pm /_6
Lactate (mmol/l)	0.98 \pm /_0.11		1.09 \pm /_0.14	1.07 \pm /_0.12	1.07 \pm /_0.11
Sedation score	2.65 \pm /_0.27	4.65 \pm /_0.42	4.8 \pm /_0.5	5.0 \pm /_0.29**	4.7 \pm /_0.42

*p < 0.05 3 hrs. v baseline values; ** p < 0.01 3 hrs. v baseline values

Haemodynamic effects of propofol infusion

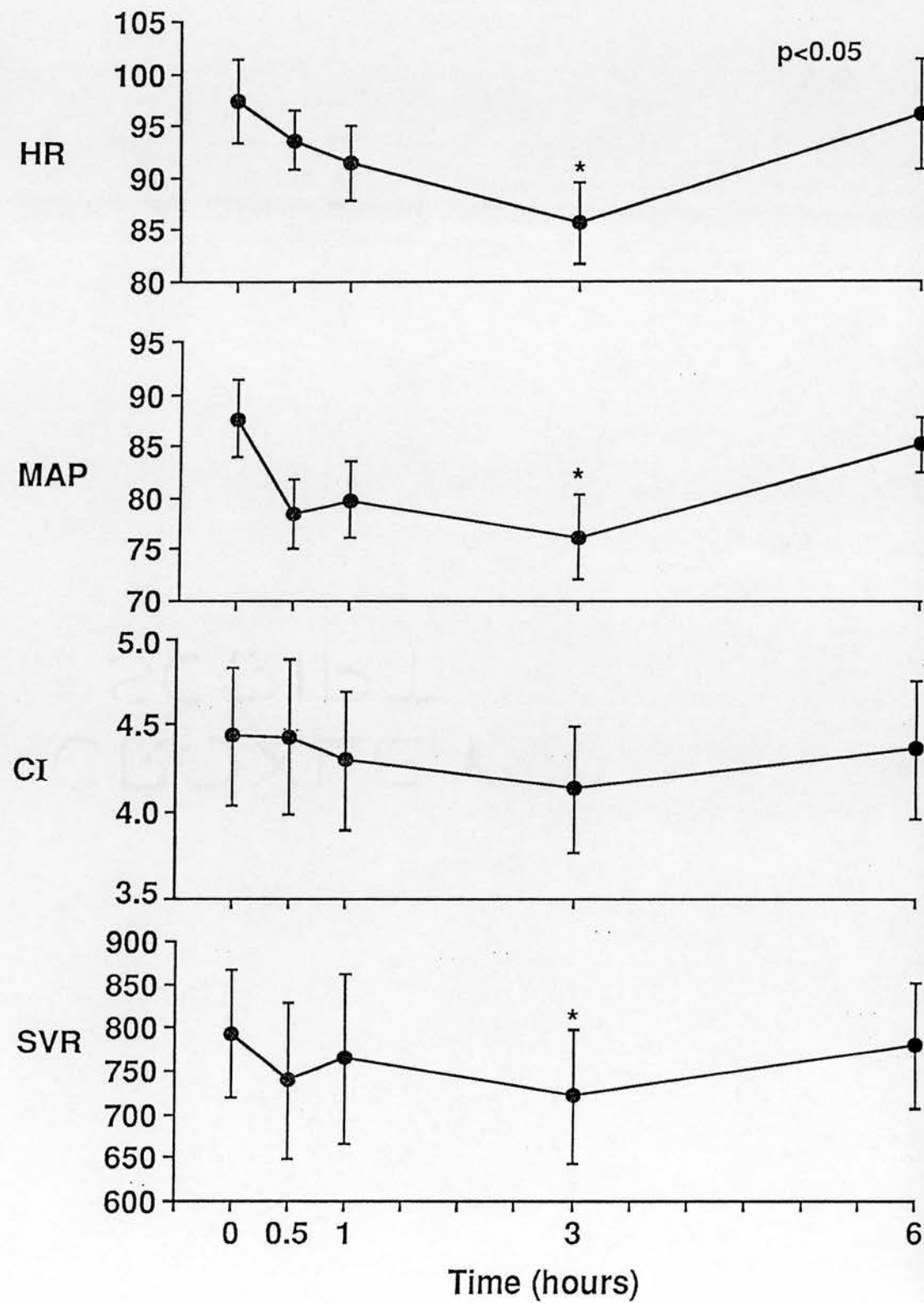


Figure 12

Sedation and oxygen transport effects of propofol

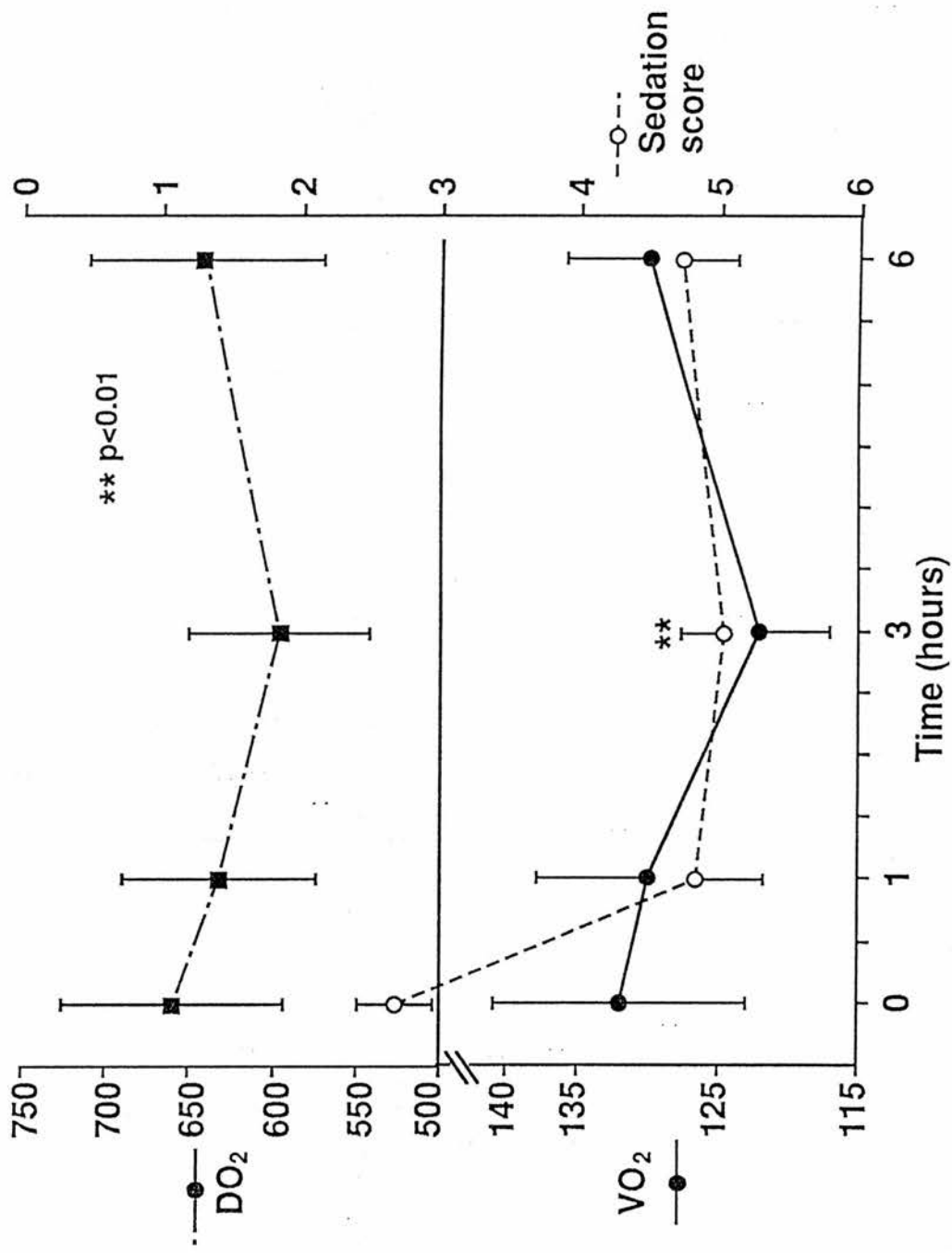


Figure 13

5.4.

Discussion

We have demonstrated that propofol given by infusion in a regimen designed to rapidly achieve and maintain a blood level of 1ug/ml is not associated with clinically significant haemodynamic or oxygen transport effects in adequately resuscitated adult critically ill patients. The haemodynamic effects of propofol anaesthesia have been extensively investigated and are well documented (Foex 1991). The induction of anaesthesia using propofol as a bolus produces a dose related reduction in blood pressure which has been attributed both to reduced cardiac output and to a reduction in SVR (Coates 1987, Gauss 1991). The mechanism of the reduction in cardiac output is a direct depression of myocardial contractility, which according to some workers may be coupled with decreased preload (Lepage 1988). Nevertheless, many investigators have found no effect on preload, attributing the fall in cardiac output to a direct negative inotropic effect alone (Coates 1987, Gauss 1991).

During continuous intravenous propofol infusion to maintain anaesthesia, SVR tends to rise back towards baseline or above, especially with surgical stimulation, and cardiac output remains below baseline (Stephan 1986, Coates 1987). HR tends to decline during propofol maintenance, due to both increased vagal tone and to the resetting of baroreceptor reflex activity (Cullen 1987). Propofol has been introduced as a sedative agent for use

in the intensive care unit. Initial studies have reported a hypotensive effect, sufficient in one study to prompt infusion rate reductions in some patients (Newman 1987). Other investigators have found little difference in cardiovascular effects when comparing propofol with midazolam (McMurry 1990). Given the accepted importance of the maintenance of supranormal cardiac output and DO_2 , whilst concurrently assuring an adequate MAP, in the treatment of patients with many types of critical illness (Shoemaker 1988), it is surprising that until now there has been little detailed data on the cardiorespiratory effects of propofol in such patients. This study has shown that propofol is well tolerated in a group of extremely sick patients, dependent on vasoactive drugs. The study protocol avoided the use of bolus doses since it is our clinical experience that even doses as low as 0.5 mg/kg given intravenously over 1 minute may lead to significant hypotension.

The infusion protocol was based on pharmacokinetic data from critically ill patients, and was geared to achieve and maintain a blood concentration of 1 μ g/ml (Albanese 1990). In fact all patients were excessively sedated at this concentration, probably reflecting their severity of illness (Apache II mean 23; range 15-31) since it has been shown that the higher a patient's Apache II score the less will be their sedation requirements (Bion 1986). At the end of the study period, propofol infusion

rates were reduced to provide a clinically appropriate level of sedation.

In no patient did the infusion rate require reduction from the protocol level as a result of severe adverse haemodynamic effects. The minimal fall in blood pressure was acceptable as the MAP remained close to the level aimed for with resuscitation, while cardiac output did not fall to a statistically significant degree.

Interestingly, stroke volume and RVEF were maintained, any reduction in cardiac output being attributable to the fall in HR. It may be that afterload reduction allowed maintenance of stroke volume despite myocardial depression. Although pooled group data on filling pressures did not show any overall change, 3 patients suffered substantial reductions of PAOP which without volume expansion would have led to reduced cardiac output.

Overall, our results show that propofol in sedative dosage is free from significant myocardial depressant effects, but that hypotension occurs due to the combination of a reduction in heart rate, and hence cardiac output, and a slight reduction in SVR, possibly as a consequence of reduced sympathetic activity. The finding of 3 patients with falls in PAOP suggests that in less well fluid resuscitated patients, venodilatation and reduced filling pressure is a potential problem. Reattainment of the baseline values of cardiac output proved straightforward, requiring fluid in 3 patients

and small increases in inotrope infusion rate in 7. The importance of achieving and maintaining a high oxygen delivery when treating critically ill patients with sepsis and ARDS has been emphasised by a number of workers, and is detailed in the previous chapters (Haupt 1985, Clarke 1991, Tuchschildt 1992). As described in chapters 2 to 4, pathological delivery dependence is due to an inability of some tissues to regulate oxygen extraction normally, and may imply a persistent tissue oxygen debt, with oxygen demand in excess of actual consumption. We have shown that this abnormality may be present despite normal blood lactate concentrations, as described in chapter 3.

In the normal human where oxygen consumption meets demand, sedation, anaesthesia, muscle relaxation and assisted ventilation should all reduce VO_2 because of the fall in requirements. Similarly, in patients with low flow conditions, such as cardiogenic shock, where critical reductions in DO_2 are present and VO_2 is maintained by avid oxygen extraction, mechanical ventilation will reduce the oxygen cost of breathing and thus tissue oxygen requirements with improvement in the oxygen supply/demand balance (Aubier 1982). It is less clear, however, how sedation affects the balance of oxygen supply, utilisation and demand in critical illnesses such as septic shock and ARDS.

Studying patients undergoing major vascular surgery, Gavin and colleagues showed a major reduction in VO_2

during anaesthesia (Gavin 1991). This reduction was associated with muscle paralysis and mechanical ventilation. It is possible that it is the active use or non-use of the respiratory muscles which influences oxygen demand and VO_2 , rather than sedation or anaesthesia.

The fact that sedation is generally associated with cardiovascular depression and thus with decreased myocardial oxygen demand, and with reduced cerebral metabolic rate for oxygen suggests that there should be a beneficial reduction in whole body VO_2 . Conversely, if the sedation also results in falls in cardiac output and DO_2 in the presence of pathological delivery dependent oxygen consumption, VO_2 may fall to a greater extent than demand, with aggravation of the oxygen shortfall. This study does not reveal a significant reduction in DO_2 associated with propofol sedation. However, there is a trend towards a parallel reduction in both DO_2 and VO_2 . Therapeutic interventions which restored DO_2 also tended to increase VO_2 , although sedation level was unchanged. No significant changes in blood lactate concentrations, which might have helped clarify the effects on tissue oxygenation, occurred.

In critically ill patients with pathological delivery dependent VO_2 , sedation may lead to reductions in VO_2 which are linked to changes in DO_2 and not oxygen demand, but in the low dosage used in this study the changes were small. A case report from Kaufman and

colleagues (Kaufman 1991) clearly demonstrated beneficial effects on tissue oxygenation and ABL concentrations from sedation in a very agitated patient. Conversely, our experience of a patient with pneumococcal septicaemia, meningitis and status epilepticus requiring propofol in high dosage (8mg/kg/hr) to achieve EEG burst suppression showed that the consequent reduction in cardiac output and DO_2 led to a tissue oxygen debt manifested by an elevated blood lactate concentration (unpublished observation). On balance, it is unlikely that changes in sedation from Ramsay level 2-3 to 5 as in this study, significantly affect the oxygen demand/consumption balance. Extreme agitation and conversely cardiac depression should be avoided. Patients in whom DO_2 is markedly reduced should be mechanically ventilated if evidence of a tissue oxygen debt is apparent as suggested by elevated lactate concentration or critically low SvO_2 .

In summary, controlled propofol sedation is well tolerated in appropriately monitored and resuscitated patients, even when they require cardiovascular support with catecholamines. It is likely that there is no clinically significant effect on global oxygen transport.

6.1.**Introduction**

The last decade has witnessed major changes in the pattern of renal replacement therapy (RRT) use, particularly in unstable and severely ill patients (Brazilay 1989). This has been in large part due to the greater haemodynamic stability which we and others have demonstrated with haemofiltration as opposed to haemodialysis (Baldamus 1983, Mackenzie 1991 ii). Since the introduction of continuous spontaneous haemofiltration by Kramer there has been a rapid adoption of haemofiltration techniques in intensive care units and acute nephrology wards (Kramer 1977). Refinements and advances in the form of continuous (spontaneous or pumped) haemodialysis and intermittent machine pumped high volume haemofiltration (HVHF) have logically followed (Geronemus 1984, Simpson 1987). The choice of treatment modality will be influenced by individual and local factors such as the patient's clinical state and underlying diagnosis, the type of unit and the availability of staff trained in the use of different types of RRT. We use HVHF with lactate containing replacement fluid for our patients with acute

renal failure (ARF) as part of multiple organ failure. It has been suggested that critically ill patients may not tolerate lactate administration because of failure to metabolise it, with resultant haemodynamic instability and worsening of metabolic acidosis (Davenport 1989).

We investigated the acid-base and cardiorespiratory effects of treatment with HVHF and lactate containing replacement fluid in critically ill patients with multiple organ failure.

6.2. Patients and methods

Twelve patients with multiple organ failure undergoing intermittent pump-driven, veno-venous HVHF were studied on one occasion each. Clinical details of the patients, including Apache II scores, are given in Table 11. Haemofiltration was undertaken as treatment for ARF in 11 patients and in an attempt to improve gas exchange in 1 patient with severe ARDS. All patients were mechanically ventilated and had femoral arterial lines and thermodilution pulmonary artery flotation catheters for standard clinical monitoring. Cardiorespiratory status was optimised before haemofiltration in all patients. Fluids and vasoactive drugs were titrated to achieve previously described therapeutic goals, (CI >4.5 l/min/m²; DO₂ >600 ml/min/m²; MAP >80 mmHg; Shoemaker 1988).

The study period was from just before haemofiltration

Table 11

Clinical Details

	Sex	Age	Diagnosis	Apache II	Outcome
1	F	63	Shock, rhabdomyolysis	43	S
2	F	53	ARDS, septic shock	21	S
3	M	80	Septic shock, ARDS	29	NS
4	M	63	Septic shock, ARDS	21	NS
5	F	54	Septic shock, ARDS	18	S
6	M	77	Septic shock, ARDS	41	NS
7	F	58	Septic shock	27	S
8	M	72	Acute pancreatitis, septic shock	20	NS
9	F	68	Candida, septic shock, ARDS	29	NS
10	F	65	Septic shock, ARDS	25	NS
11	M	73	Septic shock, ARDS	33	NS
12	M	68	Septic shock, liver failure	21	NS

until one hour after its finish. During this period there were no changes to sedation, ventilator settings or increases in catecholamine infusion rates, although 3 patients required reductions in these because of rising blood pressure during HVHF. Extra fluid administration by bolus was not required in any patient.

Haemofiltration was performed using a Gambro AK 10 system with a FH 77 hollow fibre filter and vascular access was through a double lumen catheter in an internal jugular or subclavian vein (Gambro AB, Lund, Sweden). A blood flow rate of 200-300 ml/min and transmembrane pressure of 300-400 mmHg were used to achieve an initial filtration rate of 100-120 ml/min, although the filtration rate tended to fall as the treatment progressed. Anticoagulation was with heparin administered into the afferent limb of the circuit to achieve an activated clotting time (ACT) 30s above baseline, or over 180s. The replacement fluid was Haemofiltrisol 22 (Gambro) containing lactate 45 mmol/l, Na^+ 140 mmol/l, Ca^{++} 1.6 mmol/l, Mg^{++} 0.75 mmol/l, Cl^- 100 mmol/l with potassium added as clinically indicated. The mean duration of treatment was 3hrs 50mins (range 2 hrs 30 mins to 6 hrs 15 mins) and mean lactate infusion was 696mmol (range 450 mmol to 1080 mmol).

Prior to haemofiltration a full cardiorespiratory profile was obtained as described in Chapter 2.

Oxygen tension (PO_2), oxyhaemoglobin saturation (SO_2), carbon dioxide tension (PCO_2), hydrogen ion

concentration ($[H^+]$) and haemoglobin concentration were measured in arterial and mixed venous blood. At the time of blood sampling 1.5ml of arterial blood was placed into pre-weighed glass tubes containing 5ml 5% perchloric acid, immediately refrigerated and subsequently analysed for lactate by the method described in Chapter 2. All measurements were repeated hourly during HVHF and at 1 hour after treatment. Statistical analysis was by a Wilcoxon signed rank sum test comparing pretreatment values with those at each hour during and following HVHF. All results are expressed as mean \pm SEM. Differences were deemed significant with $p < 0.05$.

6.3. Results

The results for the ARDS patient were similar to the 11 ARF patients, and the results are presented together, and summarised in Tables 12 and 13. Haemofiltration was well tolerated in all patients. There were minor falls in MAP, CI and DO_2 but these were not statistically significant. SVRI and VO_2 showed increases during the treatment, but these changes were not significant. Lactate concentrations rose quickly (Pre 1.7 ± 0.3 mmol/l; 1hr 5.6 ± 0.4 mmol/l; $p < 0.0001$) and were still elevated, although not significantly (2.6 ± 0.4 mmol/l; $p = 0.06$), 1 hour after HVHF. Baseline arterial and mixed venous $[H^+]$, $[HCO_3^-]$ and pCO_2 were not significantly different. Arterial and mixed venous $[H^+]$ tended to

Table 12

Effects of HVHF on cardiorespiratory status

	Pre	1 Hour	3 Hours	1 Hour Post	
HR (beats/min)	106.4 ⁺ / _{-3.9}	103.2 ⁺ / _{-3.9}	107 ⁺ / ₋₅	106 ⁺ / _{-4.7}	NS
CI (l/min/m ²)	4.8 ⁺ / _{-0.2}	4.1 ⁺ / _{-0.3}	4.2 ⁺ / _{-0.3}	4.7 ⁺ / _{-0.3}	NS
CVP (mmHg)	15.8 ⁺ / _{-1.2}	13.3 ⁺ / _{-1.2}	14.5 ⁺ / _{-1.2}	14.8 ⁺ / _{-1.6}	NS
MAP (mmHg)	75.8 ⁺ / _{-3.9}	72 ⁺ / _{-4.1}	73.6 ⁺ / _{-4.5}	76.3 ⁺ / _{-3.9}	NS
PAOP (mmHg)	14.3 ⁺ / _{-0.9}	13.5 ⁺ / _{-0.9}	13.7 ⁺ / _{-0.9}	14.8 ⁺ / ₋₁	NS
SVRI (dynes sec/cm ⁵ m ²)	1034 ⁺ / ₋₆₉	1183 ⁺ / ₋₁₀₇	1197 ⁺ / ₋₁₀₅	1097 ⁺ / ₋₈₂	NS
DO ₂ (ml/min/m ²)	718 ⁺ / ₋₄₄	641 ⁺ / ₋₄₅	647 ⁺ / ₋₄₇	684 ⁺ / ₋₄₈	NS
VO ₂ (ml/min/m ²)	150 ⁺ / _{-7.25}	149 ⁺ / ₋₇	160 ⁺ / ₋₈	154 ⁺ / ₋₆	NS

Table 13

Effects of HVHF on lactate, blood gas and acid base status.

	Pre	1 Hour	3 Hours	1 Hour Post
Lactate	1.7 ⁺ / _{-0.3}	5.6 ⁺ / _{-0.4} ***	6.9 ⁺ / _{-0.3} ***	2.6 ⁺ / _{-0.4}
H ⁺	50 ⁺ / ₋₃	51 ⁺ / ₋₃	48 ⁺ / _{-2.7}	43 ⁺ / ₋₂
Arterial				NS
PCO ₂	6.2 ⁺ / _{-0.5}	5.7 ⁺ / _{-0.4}	5.6 ⁺ / _{-0.4}	6.1 ⁺ / _{-0.4}
PO ₂	13 ⁺ / ₋₁	13 ⁺ / ₋₁	15 ⁺ / _{-1.5}	13 ⁺ / _{-1.5}
HCO ₃	23.7 ⁺ / ₋₂	20.9 ⁺ / ₋₁	21.9 ⁺ / ₋₁	25.8 ⁺ / ₋₁
SO ₂	94 ⁺ / ₋₁	94 ⁺ / ₋₁	95 ⁺ / ₋₁	94 ⁺ / ₋₁
				NS
H ⁺	51 ⁺ / ₋₃	53 ⁺ / ₋₃	49 ⁺ / ₋₃	45 ⁺ / ₋₂
Mixed				NS
PCO ₂	6.9 ⁺ / _{0.5}	6.2 ⁺ / _{-0.5}	6.3 ⁺ / _{-0.6}	6.7 ⁺ / _{-0.6}
PO ₂	5.4 ⁺ / _{-0.3}	5.3 ⁺ / _{-0.3}	5.2 ⁺ / _{-0.3}	5.2 ⁺ / _{-0.2}
Venous				NS
HCO ₃	23.3 ⁺ / ₋₂	20.7 ⁺ / ₋₁	22.2 ⁺ / _{-1.3}	25.8 ⁺ / ₋₁
SO ₂	74 ⁺ / ₋₂	72 ⁺ / ₋₂	72 ⁺ / ₋₂	73 ⁺ / ₋₂
				NS

*** p<0.001

fall, and $[\text{HCO}_3^-]$ tended to rise although none of these achieved statistical significance. There were no significant changes in blood gas measurements. Four of the 12 patients survived.

6.5. **Discussion**

In this and a previous study (Mackenzie 1991 ii) we have demonstrated that HVHF is well tolerated in a potentially unstable group of patients with multiple organ failure. In our previous group of patients, there were significant falls in CVP and CI with blood pressure maintained by vasoconstriction. In the present study we have not confirmed these findings, and this probably reflects the clinical and haemodynamic heterogeneity of small groups of critically ill patients. What we have confirmed is the haemodynamic stability of HVHF in these patients.

The mechanisms for the handling of blood lactate in critically ill patients with multiple organ failure are widely discussed, but are still incompletely understood (Simmons 1978, Rashkin 1985, Cohen 1991). The ABL concentration is a reflection of the balance of lactate entering the circulation (exogenous or endogenous) and lactate removal, mainly by the liver. As detailed in chapters 3 and 4, in shock, sepsis and ARDS, splanchnic blood flow is abnormal and the ability for the tissues to utilise oxygen is impaired (Duff 1969, Dahn 1988). In view of this there are theoretical concerns over the

ability of the liver to handle the large, acute lactate load which is administered during HVHF. Davenport and colleagues have shown that in their patients with ARF, with or without liver failure, there were significant falls in MAP and serum (arterial) bicarbonate (Davenport 1989). In the hepatorenal group there was a significant rise in $[H^+]$. In contrast, our studies have not shown any significant hypotension, although in both of our studies the initial MAP was lower than in their ARF group, and equivalent to that of the hepatorenal group. In our current study we have shown that there is no deterioration in arterial or mixed venous acid-base status during HVHF, despite higher peak lactate concentrations than in Davenport's study at 6.9 ± 0.3 mmol/l at 3hrs.

We chose to measure mixed venous gases and acid-base status based on the studies of Adroque (Adroque 1989) and Weil (Weil 1986), which have suggested that the central or mixed venous sampling site is more sensitive to the acid-base changes in the microcirculation, than is systemic arterial sampling. We have shown that this is not the case for blood lactate concentrations, as detailed in Chapter 2 (Nimmo 1993 i). In the current study we showed no significant difference between arterial and mixed venous acid-base parameters throughout the study period, and there were no adverse effects on $[H^+]$ or $[HCO_3^-]$ in our patients. It has been suggested that the adverse acid-base

responses and hypotension seen in previous studies may be due to reduced tissue oxygen delivery (Davenport 1989). This seems likely, although the absence of appropriate monitoring of flow and oxygen transport in Davenport's study allows no more than speculation on this point.

It is widely accepted that MAP may be reasonably maintained despite low cardiac filling pressures, CI and DO_2 . In our patients these variables were measured prior to haemofiltration, and appropriate resuscitation was carried out in an attempt to increase CI and DO_2 whilst maintaining MAP near normal. In contrast to our study population, that of Davenport and co-workers contained 6 patients with overt hepatic failure. These patients are notoriously resistant to resuscitation, even with high doses of vasopressors. It would, however be of interest to study this group of patients in the manner which we have described. The addition of acetyl cysteine infusion in those with hepatic failure secondary to self-poisoning with paracetamol, in view of its documented benefits on haemodynamics and oxygen transport in these patients, would also be of considerable interest (Harrison 1991).

We conclude that HVHF with lactate-containing fluid in critically ill patients is appropriate and that no deterioration in acid-base status or cardiorespiratory function accompanies this treatment, despite theoretical

objections concerning the exogenous lactate load. This is likely to be a reflection of prior resuscitation, aiming to maintain high DO_2 and normal MAP.

7.1. Introduction

Previous studies have documented activation of protease enzymes such as the plasma kallikrein-kinin system in endotoxaemia and sepsis, and have shown that activation is associated with important biological effects (Colman 1977). There is a clear association between endotoxaemia and sepsis, and activation of the plasma kallikrein-kinin system as shown in septic shock (Colman 1977). A number of investigators have described reduced plasma concentrations of plasma prekallikrein, increased "kallikrein-like activity", and decreased kallikrein inhibitory activity, probably as a result of endotoxin-induced activation of Hageman factor (Webster 1959, Neiss 1968). Kinins probably mediate several important features of septic shock, a number of their proven effects being implicated in the pathophysiology of the syndrome. In particular, kinins are potent systemic vasodilator peptides, but cause pulmonary vasoconstriction in most species (Mason 1970). They cause increased capillary permeability, and stimulate release of arachidonic acid from cell membranes, leading to increased prostaglandin and thromboxane synthesis (Mason 1970). It is not certain, however, whether the

reduced plasma prekallikrein in sepsis is wholly due to kallikrein-kinin system activation, or whether it in part reflects reduced prekallikrein synthesis (O'Donnell 1976). It is also unclear whether kallikrein-kinin activation is directly involved in the pathogenesis of septic shock. Experimental studies involving the response to endotoxin infusion have failed to support this hypothesis, although because of the lack of specific, potent kallikrein-kinin antagonists, direct evidence is lacking (Marceau 1983, Cumming 1984). Aprotinin is a broad-spectrum serine protease inhibitor with some kallikrein-inhibitory activity (Kaplan 1977). The affinity of aprotinin for kallikrein is less than that for some proteases (Kaplan 1977), and it is now recognised that previous studies using this agent have used doses of aprotinin which inhibit plasma kallikrein poorly, if at all (Fritz 1983). We chose to investigate the effects of aprotinin, at a dose known to inhibit the plasma kallikrein-kinin system maximally, in a large animal (ovine) model of intra-peritoneal and systemic sepsis which has been shown to reproduce the important features of clinical septic shock (Richmond 1985). Sepsis and acute renal failure are frequently associated, and up to 50% of cases of acute renal failure are due to septic shock (Wardle 1982). The pathogenesis of this syndrome is poorly understood, but some investigators have suggested that the systemic arterial vasodilatation which occurs in early sepsis may be the principal

stimulus causing the kidney to retain salt and water (Beaman 1987), leading to "functional" renal failure associated with reduced glomerular filtration and sodium retention (Cumming 1988). Several studies have suggested that this renal response may reflect renin-angiotensin activation, together with reduced activity of the intra-renal tissue kallikrein-kinin system, which normally acts to preserve renal function during hypoperfusion (Richmond 1985, Cumming 1988). It was therefore important to discover whether aprotinin treatment, which could further reduce renal kallikrein activity, adversely affected renal function in intra-peritoneal and systemic sepsis.

The overall hypothesis of the studies was that aprotinin therapy would prevent or ameliorate hypotension and systemic vasodilatation in the initial study, and that it might reverse hypotension and systemic vasodilatation in the study of intervention in established septic shock. It was hypothesised that these beneficial actions on the systemic circulation, and thus renal perfusion, would outweigh any adverse effect of local renal tissue kallikrein inhibition. A similar effect has been demonstrated by ourselves and others using the potentially nephrotoxic catecholamine vasoconstrictors noradrenaline and adrenaline in hyperdynamic septic shock (Cumming 1989 ii, Redl-Wenzl 1993).

7.2.

Materials and methods

The technique of surgical induction of peritonitis was modified from that of Wichterman (Wichterman 1980). Twelve healthy sheep aged 12-18 months and weighing 40-50 kg underwent general anaesthesia with halothane, nitrous oxide and oxygen, to allow cannulation of the common carotid artery with a 16 F single lumen line, and the pulmonary artery via the external jugular vein with a triple lumen balloon-tipped, thermodilution PAC. The bladder was catheterised per urethra. After recovery from anaesthesia, animals were housed in metabolic cages and volume loaded with 6 litres of compound sodium lactate solution intravenously over 24 hours. Crystalloid was used as it was the fluid used in the initial studies validating the model (Richmond 1985). After control haemodynamic measurements and blood and urine sampling, animals underwent a second general anaesthetic when peritonitis was induced by caecal ligation and puncture. Post-operatively all animals received 50 mg pethidine IV, and were continued thereafter on an IV infusion of pethidine at a rate of 50 mg/6 hrs. IV infusion of compound sodium lactate (150 ml/hr) continued for the duration of the experiment, and the rate of additional fluid supplements was adjusted to maintain the previously determined optimal PAOP for individual animals. Haemodynamic measurements were made hourly, and blood and urine collections were made 4 hourly after the induction of sepsis.

Animals were supervised continuously during the studies. Any animal seen to be restless, agitated or showing other evidence of discomfort despite pethidine infusion was sacrificed immediately by IV bolus injection of pentobarbital. Animals surviving through 12 hours were sacrificed in the same manner. An open renal biopsy was taken at the time of death. Haemodynamic variables measured were those detailed in Chapter 2 and included MAP, CVP, PAM, PAOP, CI and SVRI. Blood samples were drawn through the aortic cannula. Plasma creatinine, sodium and osmolarity were measured by standard autoanalyser techniques, and plasma renin activity was measured by radioimmunoassay. Urine volume was recorded and urine creatinine, sodium and osmolarity measured. Urinary kallikrein was assayed as detailed in Chapter 2. Kidney tissue was examined by light microscopy using standard methods (Solez 1980).

Protocol Study 1: In the treatment group (n=6), aprotinin was infused intravenously, commencing 30 minutes after the completion of the surgical induction of peritonitis. A loading dose of one million kallikrein inhibitor units (KIU) was given, followed by a continuous infusion of 200,000 KIU/hr for the duration of the study. In control animals (n=6), the saline vehicle alone was infused at the same rate.

Protocol Study 2 (intervention): Peritonitis and septic shock were induced as described above (n=5). Once volume-resistant hypotensive septic shock had developed

as determined by a fall in MAP >40 mmHg, unresponsive to further volume loading, a bolus of aprotinin, one million KIU, was given IV followed immediately by a continuous infusion of one million KIU/hr for the duration of the study.

Statistics

Study 1: for the purposes of analysis, for each variable, the values included were those values at baseline (presepsis) and observations made at 4 and 8 hours postoperatively and at the termination of the study (12 hours postoperatively). Two-way analysis of variance for repeated measures was used to assess the significance of changes with time for each variable in the treatment and control groups, and the significance of between-group (aprotinin treatment) effects. Values for $p < 0.05$ were considered significant. Results are shown as mean \pm SEM.

Study 2: Two-way analysis of variance for repeated measures was used to assess the significance of changes with time for each variable, comparing time points with baseline. Significance was defined as above.

7.3. Results

As in the studies performed to establish and validate this experimental model (Richmond 1985, Cumming 1988), all animals developed a polymicrobial peritonitis and bacteraemia; organisms grown on blood culture included

Escherichia coli, *Serratia*, *Enterobacter*, *Pseudomonas* and *Bacteroides* species, and autopsy showed generalised purulent peritonitis and an inflammatory mass in the right lower quadrant. PAOP was maintained in the range 10-20 mmHg during the study, and adjusted to the optimal level with respect to cardiac output.

Study 1: Results for systemic haemodynamics and renal function at baseline and during the study are shown in Figures 14 to 19. In the control animals (n=6) there were significant falls with time in blood pressure (Figure 14) and systemic vascular resistance index (Figure 16), and an early increase in mean pulmonary artery pressure (Figure 17), with a reduction in creatinine clearance (Figure 18) and fractional sodium excretion (Figure 19). None of these parameters altered significantly in the aprotinin-treated animals (n=6). Cardiac index (Figure 15) and urine volume did not change significantly with time in either group. There was a statistically significant effect of aprotinin treatment, in a two-way analysis of variance, for the parameters mean arterial pressure ($p<0.05$) and mean pulmonary artery pressure ($p<0.01$).

In the control group, urinary kallikrein excretion tended to fall during sepsis, and there was a significant increase with time in plasma renin activity (Table 14), changes which have been previously described in this model (Cumming 1988). Aprotinin treatment was associated with lower urinary kallikrein excretion

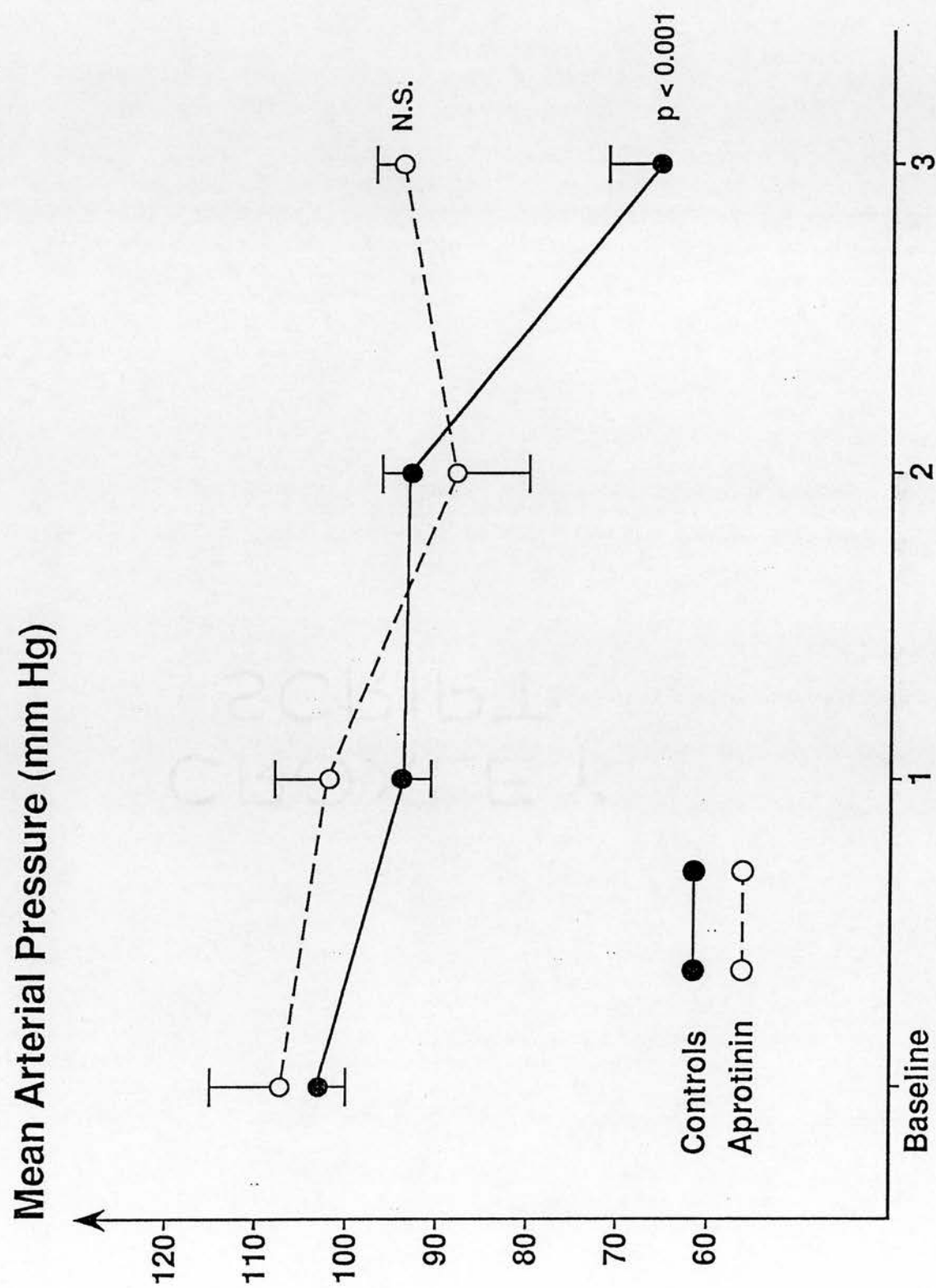


Figure 14

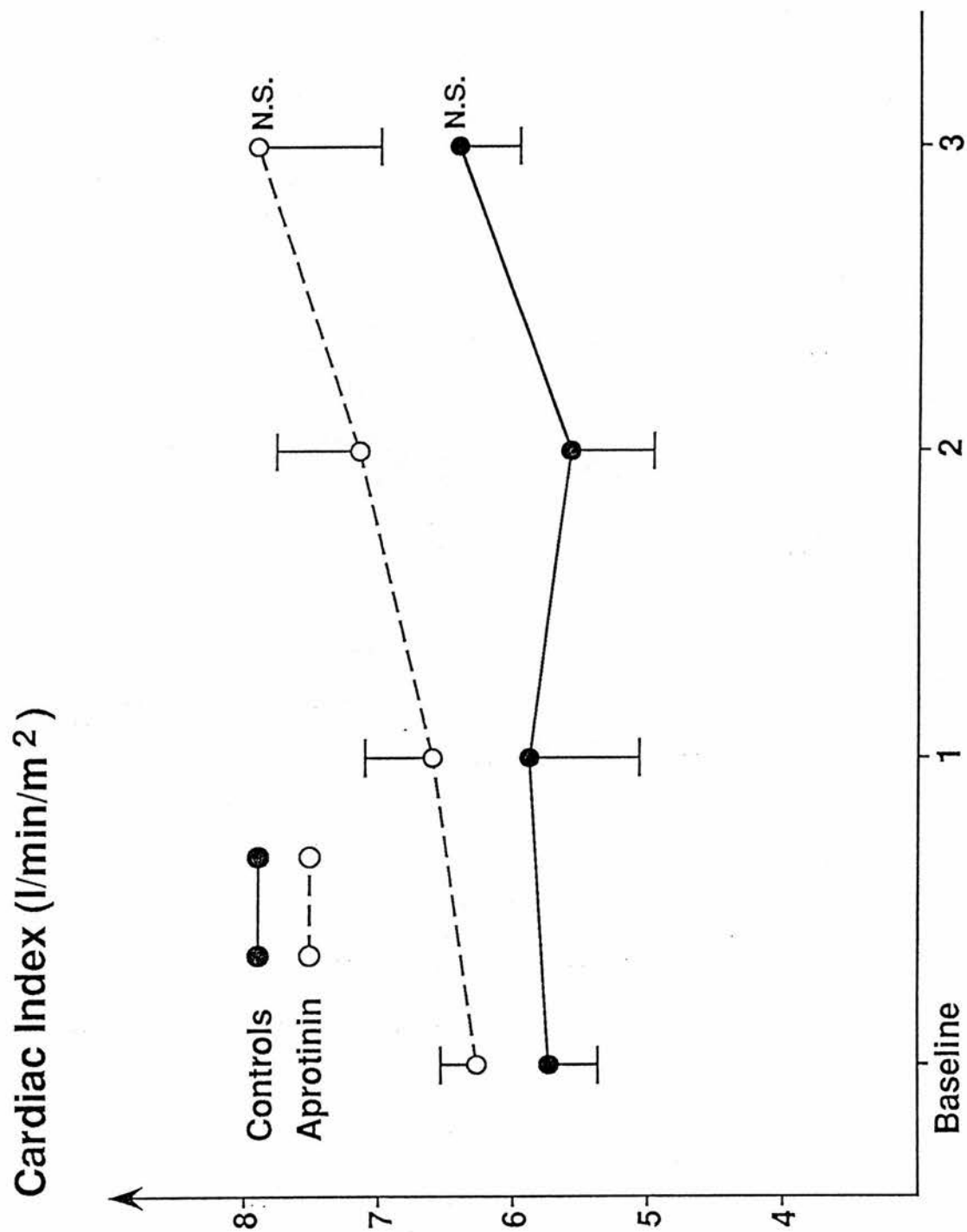


Figure 15

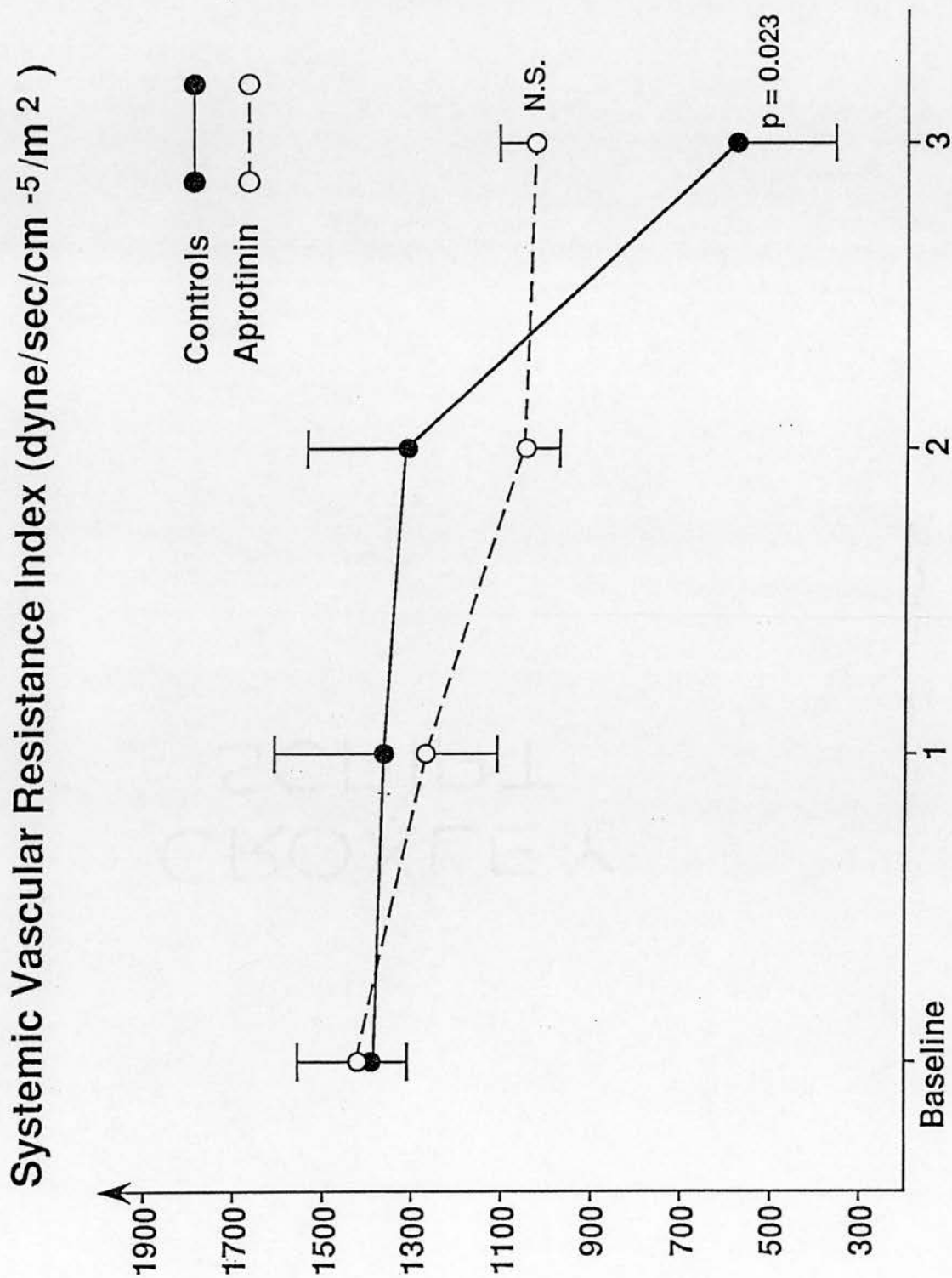


Figure 16

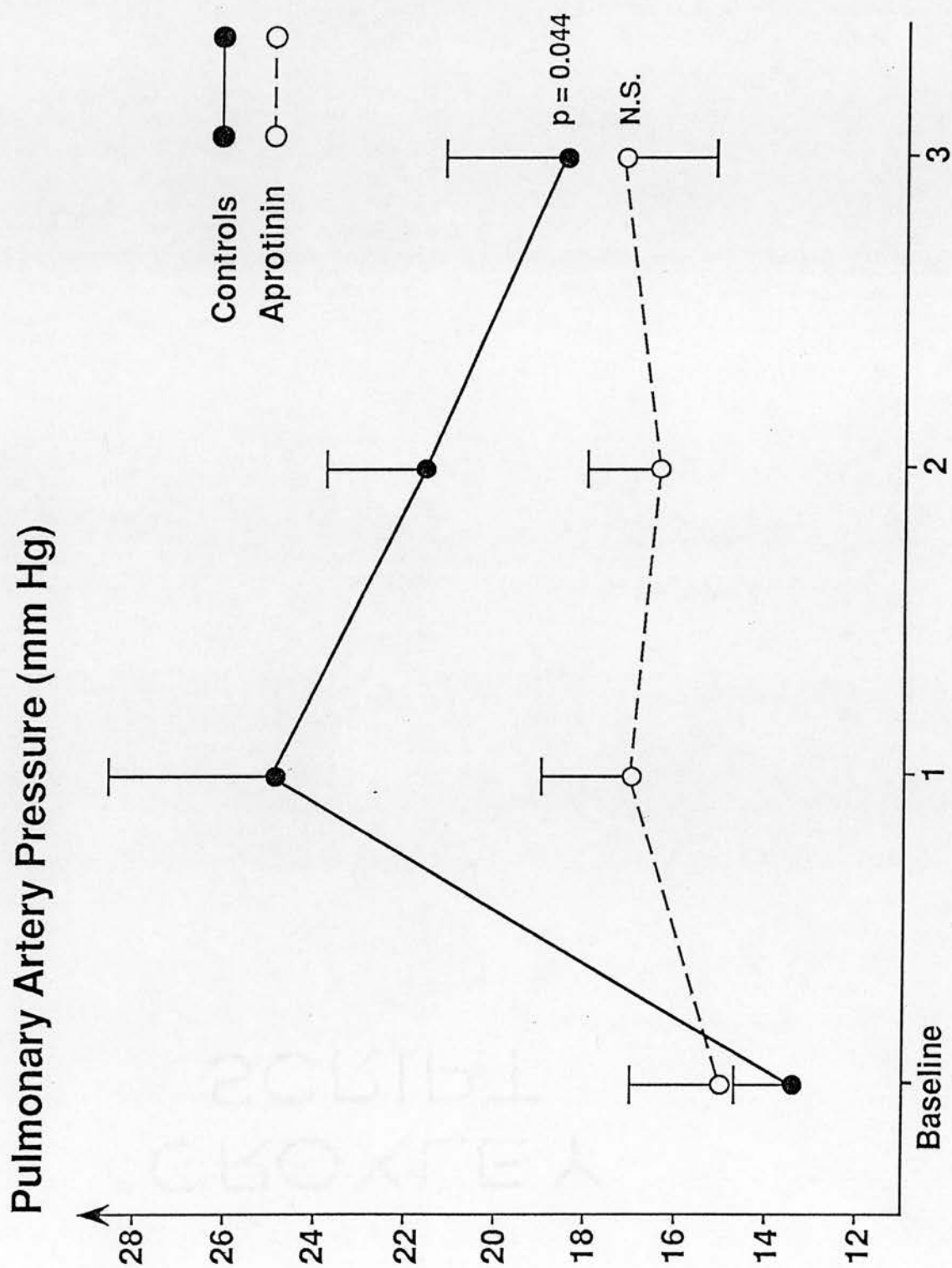


Figure 17

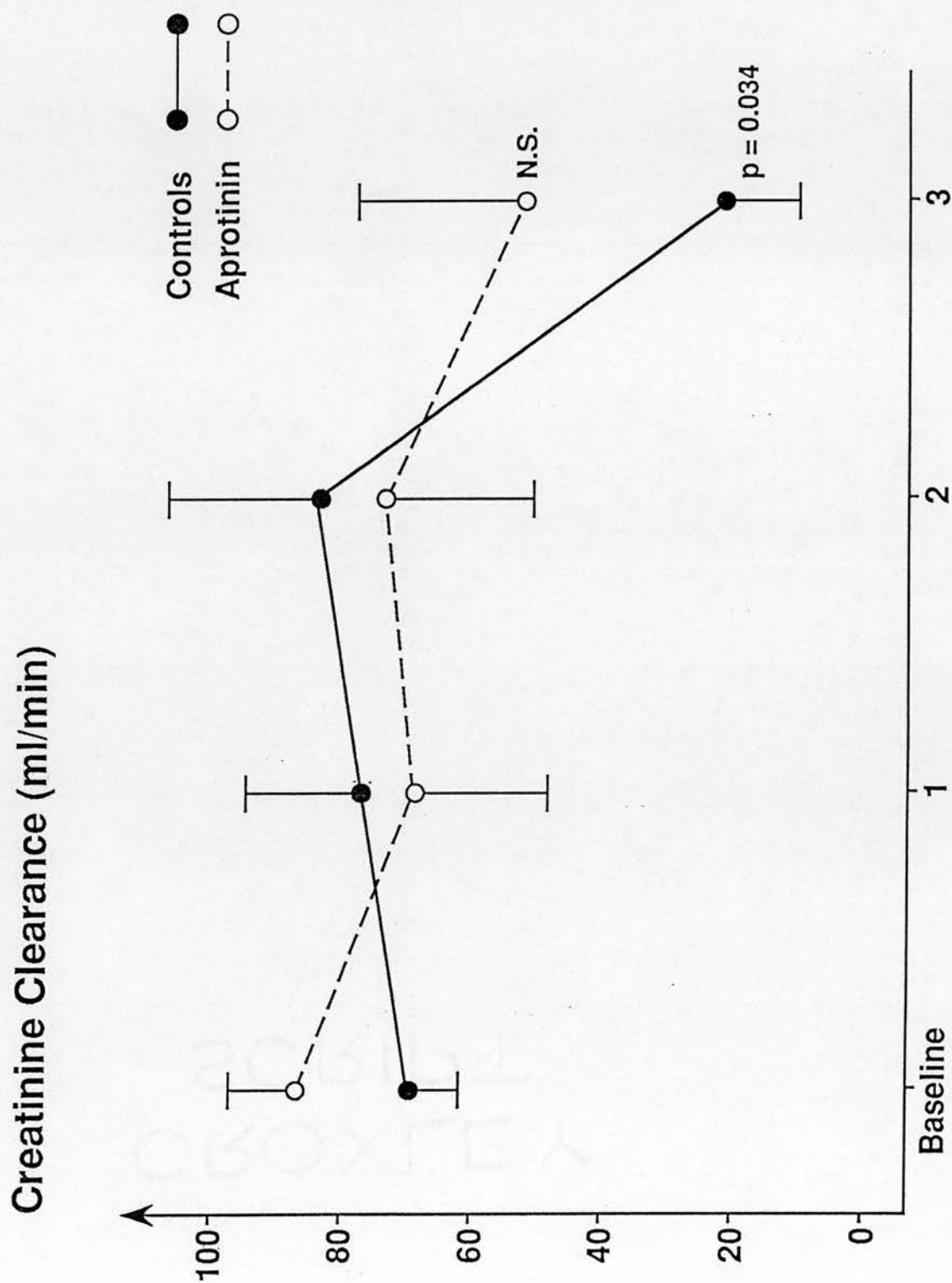


Figure 18

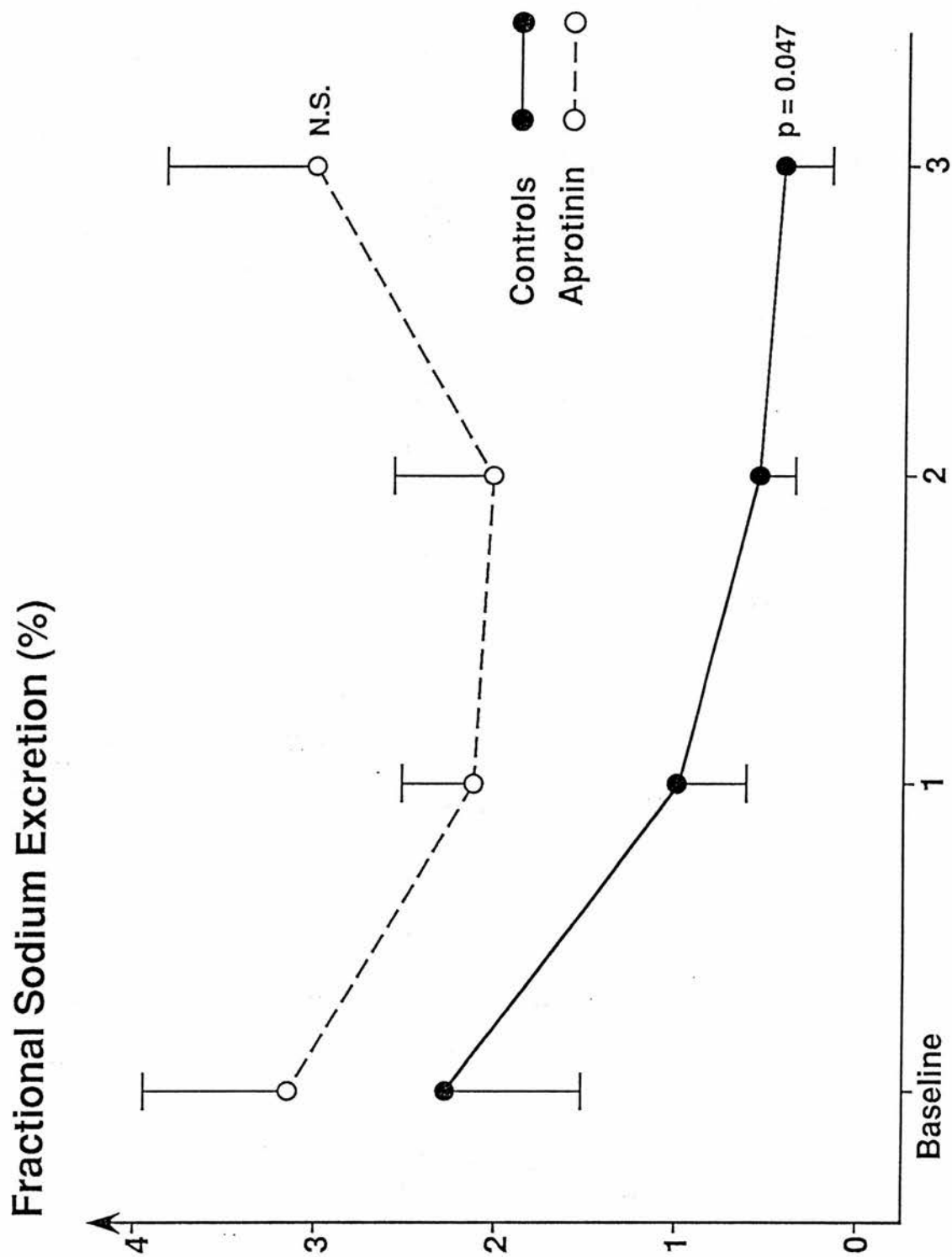


Figure 19

Table 14

Urine kallikrein excretion rate and plasma renin activity in control and aprotinin treated groups (mean \pm SEM)

	Control		Aprotinin	
	Baseline	Sepsis	Baseline	Sepsis
Urine kallikrein (nkatx10 ⁻³ /min)	2.67 ⁺ / _{-1.40}	1.67 ⁺ / _{-0.91}	1.76 ⁺ / _{-1.00}	0.70 ⁺ / _{-0.49}
Plasma renin activity (ng/ml/hr)	0.21 ⁺ / _{-0.01}	6.34 ⁺ / _{-0.92} *	0.20 ⁺ / _{-0.01}	1.78 ⁺ / _{-0.69} **
Plasma renin activity (ng/l/sec)	0.06 ⁺ / _{-0.003}	1.76 ⁺ / _{-0.25} *	0.06 ⁺ / _{-0.003}	0.49 ⁺ / _{-0.19} **

* p< 0.05 from baseline; ** p< 0.05 from controls.

during sepsis, although the difference was not statistically significant. Plasma renin activity did not rise significantly in the aprotinin treated group, and plasma renin activity was significantly lower in this group at the conclusion of the study (Table 14).

Intervention study: Results for systemic haemodynamics at baseline, following the development of volume-resistant septic shock, and during aprotinin treatment are shown diagrammatically in Figures 20-22. There were significant reductions in MAP and systemic vascular resistance index, with an immediate and rapid increase in both (Table 15), in some animals virtually to pre-sepsis levels following aprotinin (Figures 23 to 25). Cardiac index did not change significantly during aprotinin infusion (Figure 21).

No consistent or striking changes in renal histology were noted in treatment or control groups, in keeping with previous studies. Those changes which were observed included mild tubular dilatation, occasional foci of tubular regeneration and patchy interstitial infiltrates of mononuclear cells. These changes were evenly distributed between all the groups.

7.4. **Discussion**

Clinical studies of pharmacological intervention in human septic shock are complicated by lack of pre-sepsis baseline parameters, problems in assessing the evolutionary stage of the sepsis, difficulty in assessing

Systemic Vascular Resistance following induction of Septic Shock

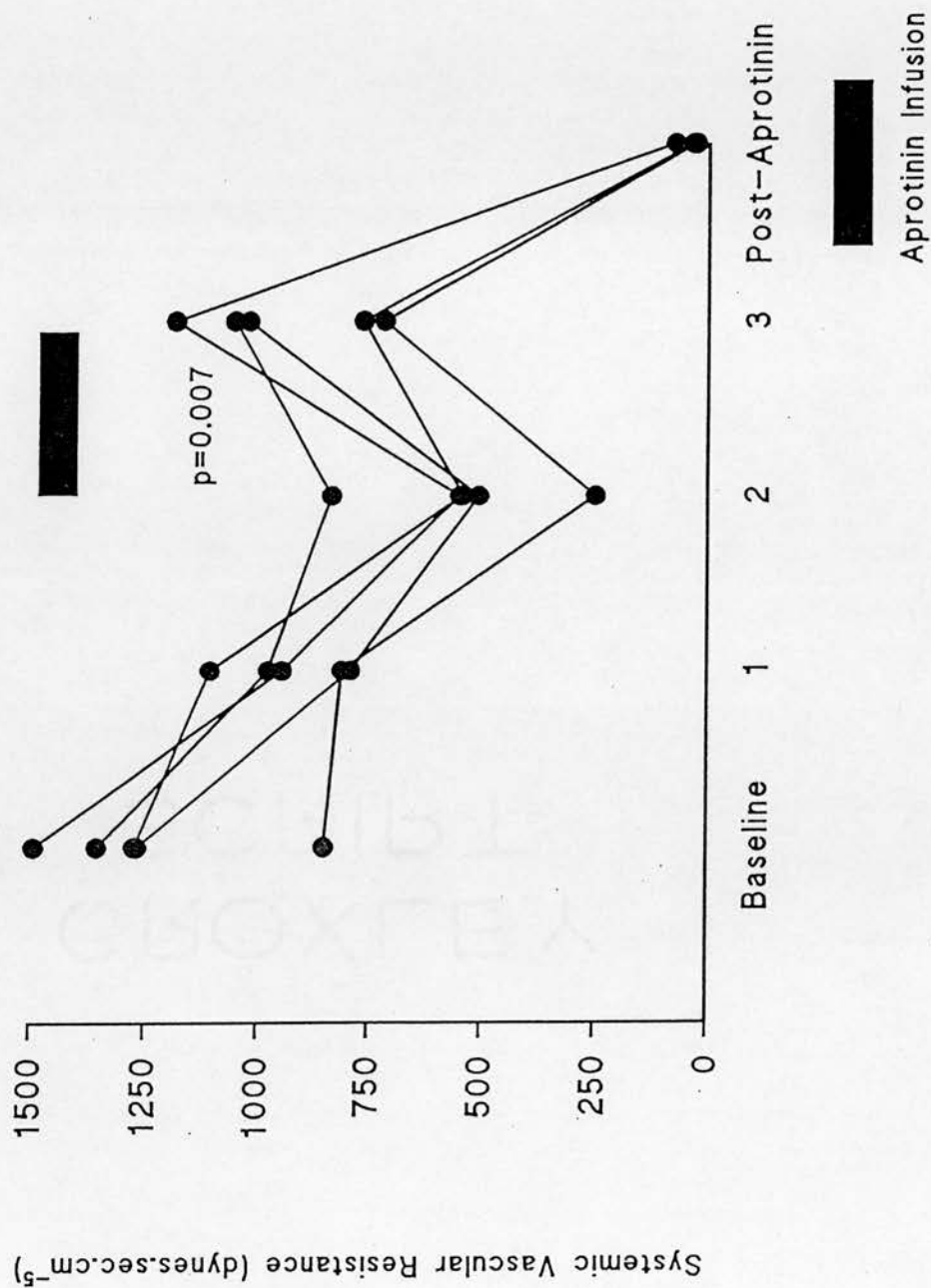


Figure 20

Cardiac Index following induction of Septic Shock

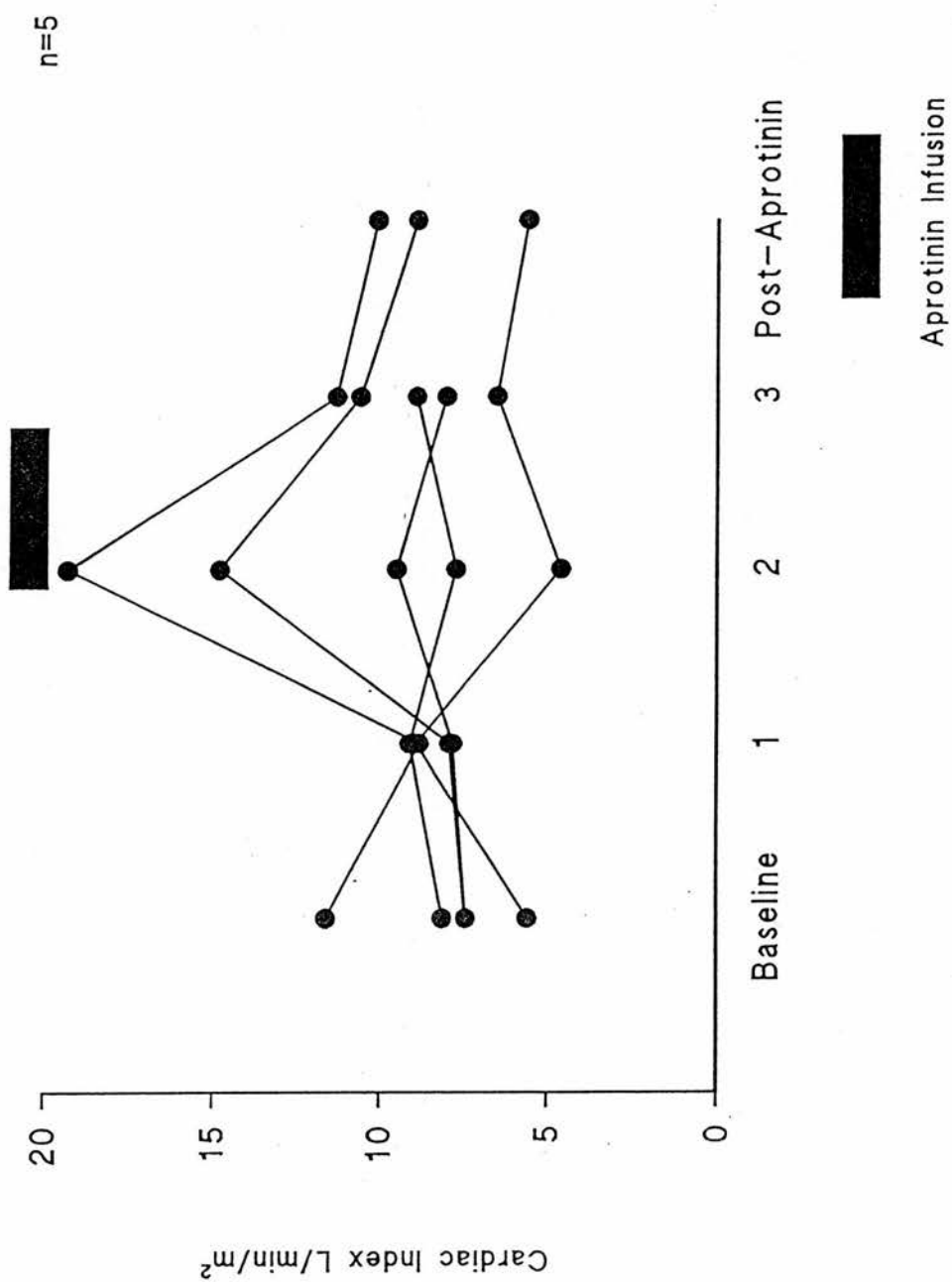


Figure 21

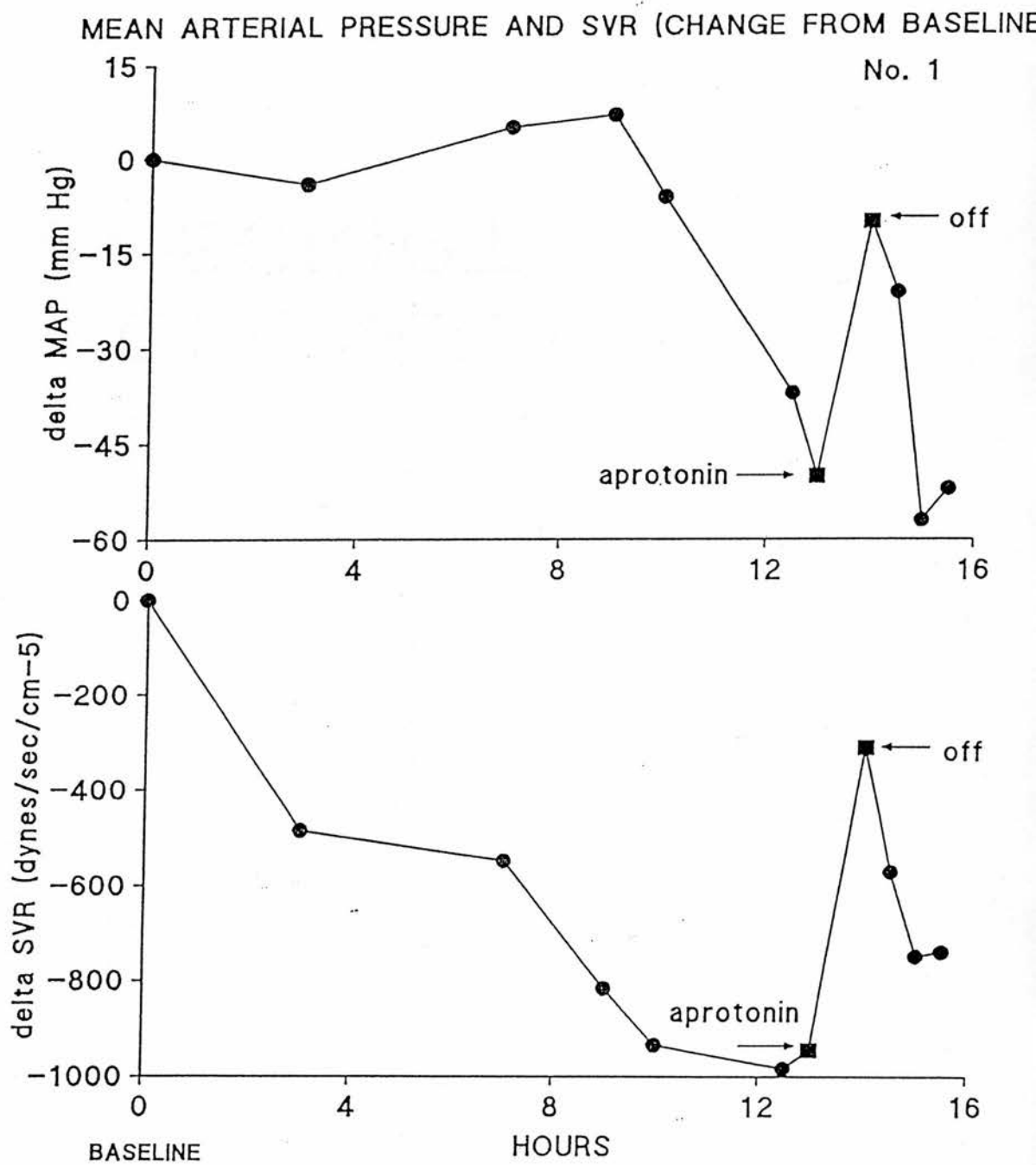


Figure 22

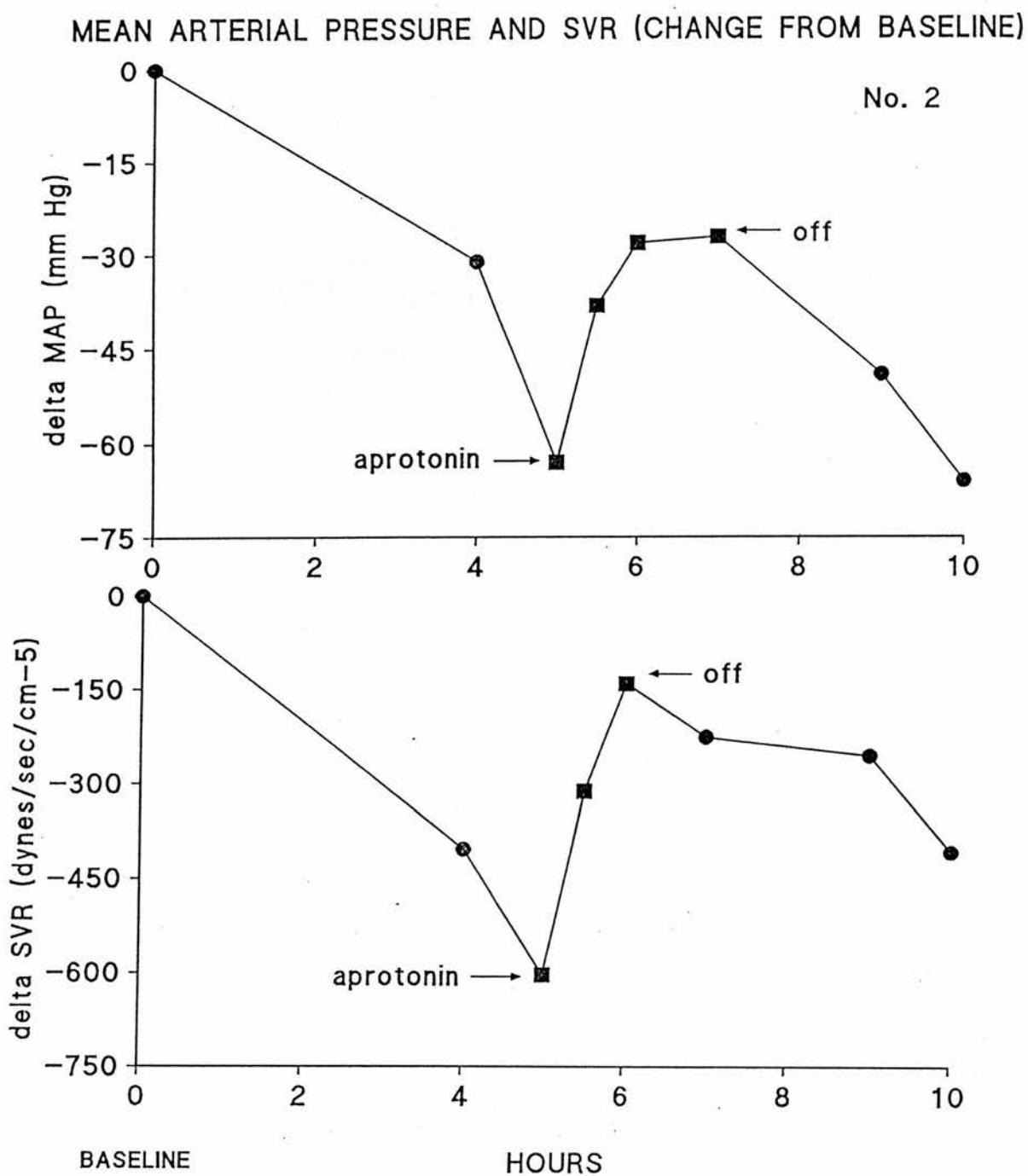


Figure 23

MEAN ARTERIAL PRESSURE AND SVR (CHANGE FROM BASELINE)

No. 3

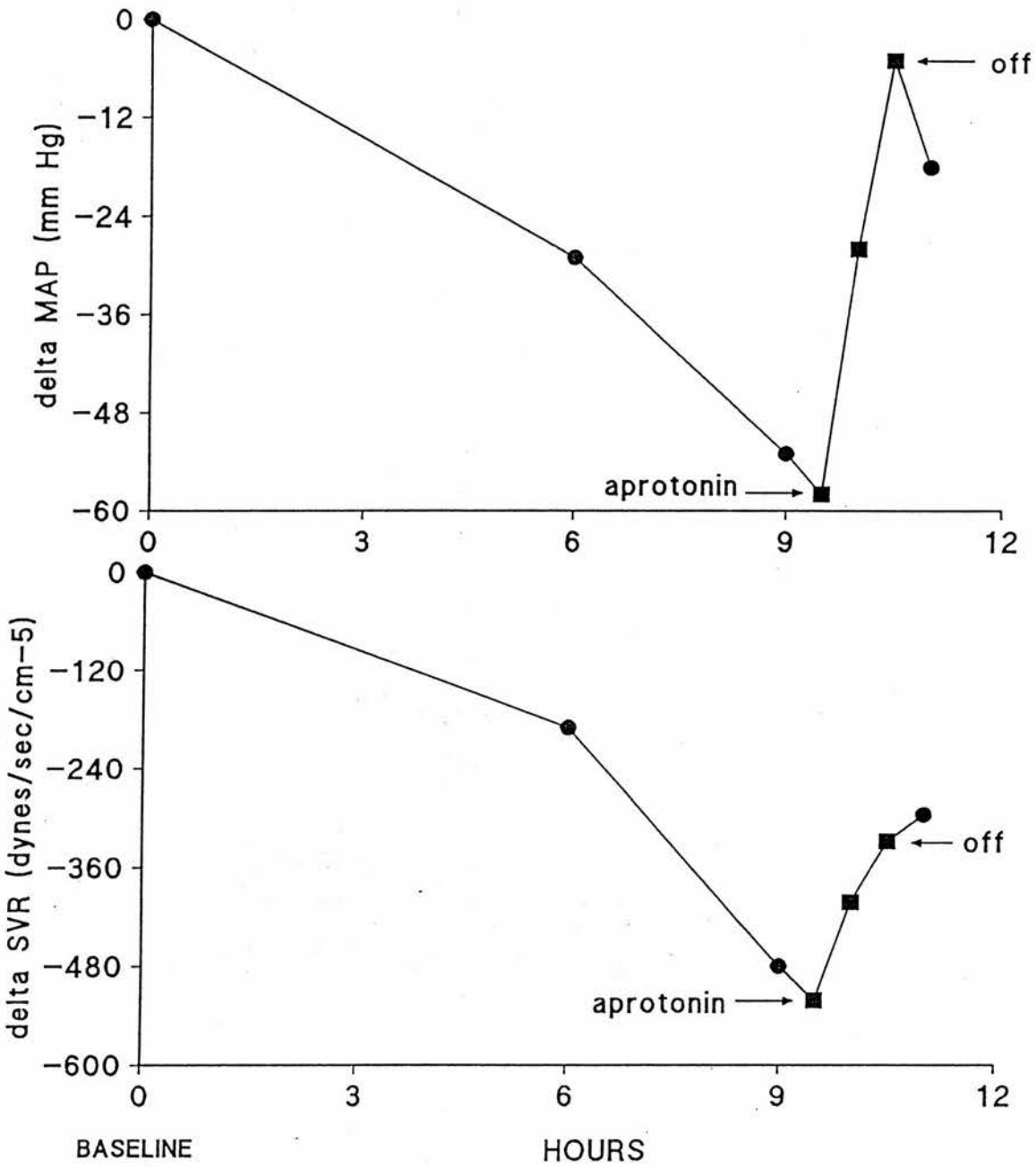


Figure 24

MEAN ARTERIAL PRESSURE AND SVR (CHANGE FROM BASELINE)

No. 5

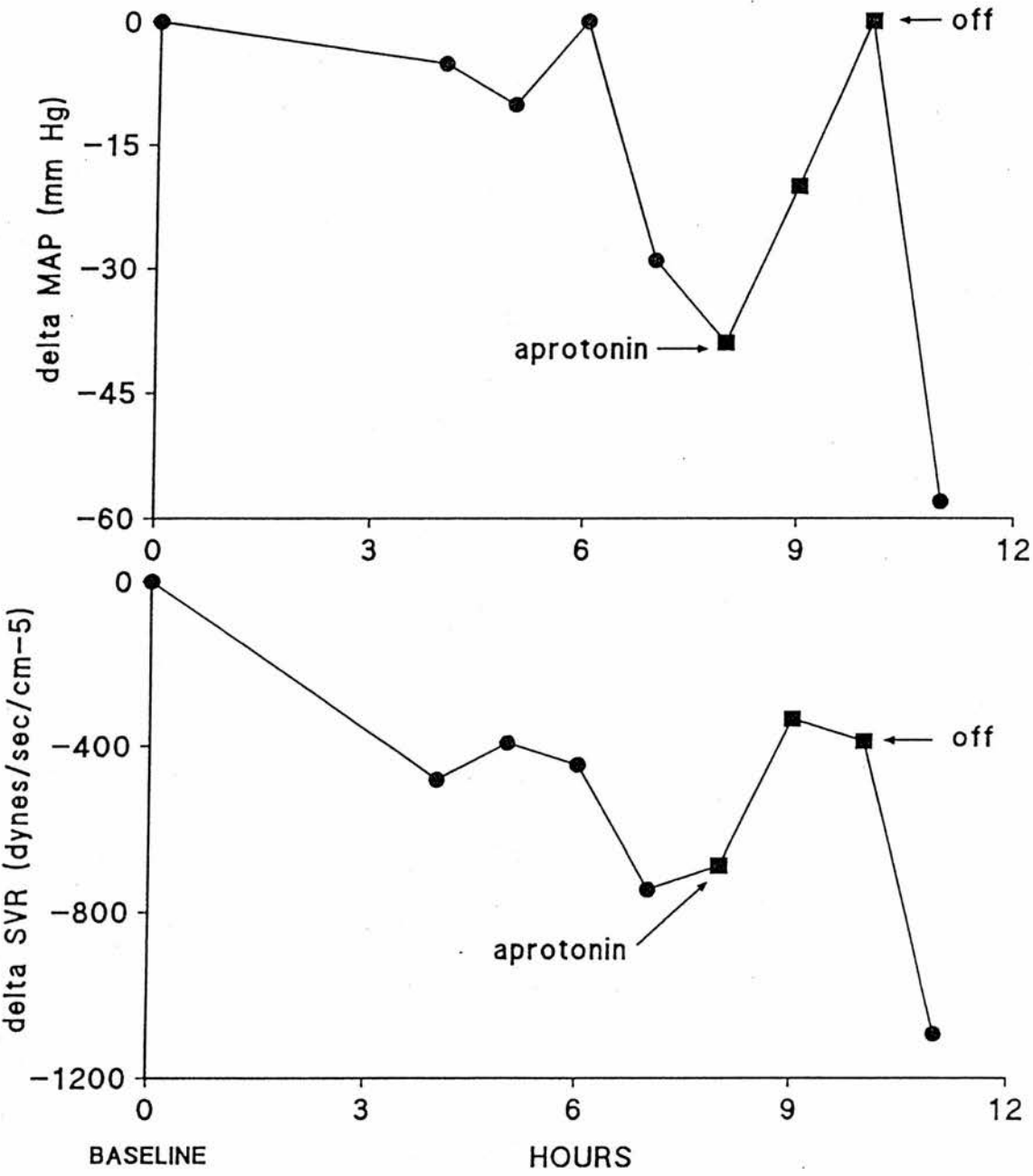


Figure 25

Table 15

Acute pressor effect of aprotinin given late in the course of septic shock.

	Change in MAP (mmHg)	Change in SVR (dyne.sec/cm ⁻⁵)
Baseline	0	0
Pre-aprotinin	- 53.8 ⁺ / _{-4.6}	- 714 ⁺ / ₋₇₅
During aprotinin	-12.6 ⁺ / _{-5.0} *	- 281 ⁺ / ₋₃₆ *
Post aprotinin	- 49.8 ⁺ / _{-10.8} **	- 636 ⁺ / ₋₁₈₀ **

*p < 0.01 vs. pre-aprotinin; **p < 0.01 vs. aprotinin.

the severity of the shock syndrome and the multiple treatments required. The experimental model of sepsis utilised in these studies overcomes these difficulties, and differs from many other experimental models of sepsis and endotoxaemia in that it reproduces the state of volume-resuscitated, hyperdynamic, and vasodilated septic shock commonly seen in clinical practice. Use of an ovine model allows detailed haemodynamic monitoring and provides sufficient sample size to permit assessment of renal function and vasoactive hormone systems. The initial events which trigger systemic vasodilatation in sepsis are unclear. However, bacterial endotoxins are potent activators of the plasma "contact systems", including the kallikrein-kinin system, through Hageman factor (Kaplan 1977). Plasma kallikrein is a serine protease, generated from an inactive precursor, prekallikrein, by the action of a Hageman factor fragment, prekallikrein activator. It acts primarily on high molecular-weight kininogen to form bradykinin (Kaplan 1977). It is known that the plasma kallikrein-kinin system is activated in septic shock, and kinins could mediate the systemic vasodilatation and increased capillary permeability seen in sepsis (Regoli 1980). We were unable to measure plasma prekallikrein or plasma kallikrein activity in this experimental model because of the very low activity of sheep kallikrein against the chromogenic substrate, S2302, used to measure plasma prekallikrein/kallikrein activity (Bonner

1981). Previous studies of patients with septic shock have shown depressed levels of plasma prekallikrein during sepsis, suggesting activation of the plasma kallikrein-kinin system, with survivors showing a return to normal during recovery (Cumming 1984). Studies of the effect of protease inhibition in the experimental model of septic shock were therefore of interest.

Aprotinin is a polypeptide protease inhibitor derived from bovine lung. It is active against a number of serine proteases including trypsin, chymotrypsin, plasmin, and plasma and tissue kallikreins. Some studies have shown benefit from its use in acute pancreatitis, and it is now widely used to inhibit blood loss during cardiac surgery (Philipp 1978, Royston 1987). Our results suggest that the hypotension and systemic vasodilatation in early septic shock are prevented by aprotinin. In addition, these changes appear to be reversed by aprotinin given as an intervention once they have become established. These effects could be due to inhibition of any of the above protease enzymes, and our results do not allow discrimination between them. It is also possible that inhibition of neutrophil-derived proteases could be involved (Niehaus 1990). Plasma kallikrein is known to be generated in septic shock, and to be associated with appropriate biological effects. Experimental intravenous injection of kallikrein induces a picture resembling septic shock, with hypotension and increased capillary permeability (Mills 1979). It is

therefore possible that the beneficial effects seen in our studies reflect, at least in part, inhibition of endotoxin-induced prekallikrein activation. Studies using more selective inhibitors of the plasma kallikrein-kinin system in small animal models of endotoxaemia support a role for kinin generation in endotoxic shock (Noronha-Blob 1991).

While aprotinin has been suggested to be useful in a wide range of disease states, it has yet to become routine therapy in any but cardiac surgery. This is probably due (at least in part) to the use of inappropriately low doses in previous studies, such as the trials in acute pancreatitis (Philipp 1978, Fritz 1983). The dose regimes used in these studies were calculated on the basis of the affinity of aprotinin for glandular kallikrein (K_i 9×10^{-11}), but the affinity of aprotinin for plasma kallikrein is considerably lower (K_i 3×10^{-8} , Fritz 1983). It is therefore likely that in previous studies, adequate inhibition of the plasma kallikrein-kinin system was not achieved (Philipp 1978). Recent work has demonstrated the feasibility and safety of using doses of aprotinin of the order of 20-fold higher than previously (Maier 1985). We have used such high doses in these studies, with apparent efficacy and no evidence of adverse effects.

As described above, the affinity of aprotinin for glandular (including renal) kallikrein is greater than for plasma kallikrein. In our studies urinary kallikrein

excretion, which is thought to reflect activity of the renal kallikrein-kinin system, was lowest while the animals were receiving aprotinin. It is believed that the renal kallikrein-kinin system, which is anatomically and functionally distinct from the plasma system, promotes renal vasodilatation and increased sodium excretion (Niehaus 1990). It is therefore theoretically possible that aprotinin could adversely affect renal function during sepsis. However, we found evidence of improved renal function in the aprotinin group in Study 1. It has been suggested that the renal vasodilator function of the renal kallikrein-kinin system only becomes important in the face of reduced renal perfusion and/or activation of the renin-angiotensin system, in a manner analogous to the role of renal prostaglandins (Nasjletti 1981). Indeed, kinins are a potent stimulus to release of renal vasodilator prostaglandins. It seems likely that in these studies, any potential adverse effect of renal kallikrein-kinin inhibition was outweighed by the improvement in systemic haemodynamics, and hence in renal perfusion, and the reduced plasma renin activity, in the treatment group in Study 1. This corresponds to situations in which potentially nephrotoxic vasoconstrictors, noradrenaline and adrenaline, have been used to reverse hypotension in hyperdynamic septic shock with documented improvement in renal function (Hesseltvik 1989, Redl-Wenzl 1993). Again, it is suggested that the improvement in global

haemodynamics outweighs any detrimental effect on the intra-renal circulation. However, aprotinin may be a more appropriate agent to use, since it is associated with less potential for indiscriminate vasoconstriction of non-pathologically vasodilated blood vessels than are the catecholamines.

In Study 1 we showed that the rise in plasma renin activity which is a typical feature of experimental septic shock, and was present in controls, was prevented by aprotinin treatment. This probably reflects the maintenance of adequate blood pressure in the treatment group. It should be noted however, that kallikrein may be an important activator of prorenin, as kinins are known to stimulate renin release, and aprotinin has been shown to reduce plasma renin activity in normal man (Seto 1983). It has been suggested that renin and angiotensin II are important in the pathogenesis of acute renal failure, and angiotensin II potentiates sympathetic nervous system activity, which may also be important in the sepsis/acute renal failure syndrome (Cumming 1988). Prevention of renin-angiotensin stimulation may therefore represent an additional beneficial effect of aprotinin treatment in sepsis. The apparent effect of aprotinin in preventing the rise in pulmonary artery pressure, maximal at 4 hrs post-operatively, is of some interest. It has been shown that the increased pulmonary lymph flow seen 2-6 hrs after administration of endotoxin to sheep is reduced by

protease inhibition (Traber 1984). It is thought to be likely that changes in pulmonary haemodynamics and permeability during sepsis reflect primarily cellular mechanisms, such as stimulation of neutrophils by complement activation (Shale 1987). Our results suggest that pulmonary hypertension may reflect activation of protease enzymes against which aprotinin is effective. These may be circulating cascade systems or could include neutrophil enzymes, although the affinity of aprotinin for neutrophil elastase and Cathepsin G is relatively low (Fritz 1983). Tissue kallikrein has recently been detected in the cytoplasm of human neutrophils (Figuerola 1989). It is known that kinins have differing effects in various vascular beds, and cause pulmonary vasoconstriction in most species (Regoli 1980). This effect of aprotinin could be beneficial in the course of septic shock, since it would be predicted to reduce lung water and improve respiratory and right ventricular performance.

From these studies we conclude that in the early stages of septic shock a number of the characteristic pathophysiological features may be due to activation of protease enzyme systems, including the kallikrein-kinin system. In an animal model developed to mimic human septic shock, administration of the protease inhibitor aprotinin benefits systemic and pulmonary haemodynamics and renal function with no adverse effects. Prospective,

randomised clinical studies are required to confirm these effects in patients, and to define the place of this agent in human sepsis.

8.1. Introduction

Throughout this thesis the proposal that tissue hypoxia is a fundamental cause of multiple organ failure is repeatedly stated. In view of this contention it is no surprise that many studies have been carried out in the quest for reliable, practical markers of tissue hypoxia in the clinical setting (Haljamae 1991). The serial measurement of arterial blood gases is an established technique used to assess gas exchange and the acid-base status of the critically ill, and to guide therapy. However, a number of investigators have shown differences between arterial and mixed venous acid-base parameters in cardiac arrest and low flow states, and have suggested that the measurement of mixed venous acid-base status may reveal otherwise unrecognised abnormalities of tissue oxygen metabolism (Weil 1986, Adroque 1989, Bleich 1989). In experimental haemorrhagic shock an inverse relationship between cardiac output and increases in $PvCO_2$ and veno-arterial PCO_2 difference ($P(v-a)CO_2$) has been demonstrated, with a decrease in both on reinfusion of shed blood (Halmagyi 1970). Hyperventilation had no effect on the elevated $PvCO_2$. Furthermore, it has been proposed that circulatory failure be defined not only in terms of oxygen lack but

also as carbon dioxide excess, manifested by an increased $P(v-a)CO_2$ difference above the normal of 0.8kPa (Johnson 1991). We have studied these relationships in human septic shock during resuscitation, and in addition measured excess lactate in a sub-group of these patients.

8.2. Patients and methods

Twenty three patients with septic shock, ventilated and invasively monitored were studied during resuscitation with fluids and vasoactive drugs, as described in Chapters 2 and 4. The mean age was 62 years (range 37 to 84), and 12 were female. Eighteen patients had aerobic Gram-negative infection (16 intra-abdominal), 8 had Gram-positive infection and one had candida septicaemia. The mean Apache II score was 22.

Protocol

All patients were intubated and mechanically ventilated, following which fluid resuscitation with colloid and blood was carried out, in conjunction with catecholamine therapy to reverse hypotension and increase DO_2 as described previously (Nimmo 1992). Full cardiorespiratory profiles were obtained prior to resuscitation, and subsequently at around 2 and 8 hours into treatment, and at the same times as acid-base measurements were made. In eleven patients excess lactate was calculated according to the equation in

Chapter 1.

Statistical analysis was carried out using the Wilcoxon signed rank test to compare paired data at baseline, 2 and 8 hours. All values are expressed as mean \pm SEM.

8.3. Results

Resuscitation resulted in global improvements of MAP, CI, SvO₂ and DO₂, with no significant change in VO₂ (Table 16). The acid-base variables are also documented in Table 16.

The initial P(v-a)CO₂ difference was at the upper limit of normal (0.8kPa), and there was no significant change with time, being 0.7kPa at both 2 and 8 hours. The relationship between individual P(v-a)CO₂ and cardiac index is depicted in Figure 26. There is no direct relationship between these variables in sepsis as there is in low flow shock.

At baseline there was no significant veno-arterial [H⁺] difference, and no significant veno-arterial [HCO₃⁻] difference. These did not change over time. Arterial [H⁺] increased along with PaCO₂ over time (44.7 ± 2.5 to 48.7 ± 2.4 nmol/l, $p < 0.01$).

Excess lactate

Excess lactate concentration had no better predictive value for delivery dependence of DO₂ on VO₂ than lactate alone (Table 16), as described in Chapter 4.

Table 16
Cardiorespiratory, arterial and mixed venous acid base
variables during resuscitation of septic shock.

	Initial	2 Hours	8 Hours
MAP (mmHg)	66.5 ⁺ / _{-2.7}	71.5 ⁺ / _{-2.8*}	78 ⁺ / _{-2.8**}
DO ₂ (ml/min/m ²)	514 ⁺ / _{-34.4}	579 ⁺ / _{-44*}	696 ⁺ / _{-68**}
VO ₂ (ml/min/m ²)	139.3 ⁺ / ₋₁₂	135.4 ⁺ / ₋₁₁	135.7 ⁺ / ₋₁₁
SvO ₂ (%)	69 ⁺ / ₋₃	73 ⁺ / _{-2*}	76 ⁺ / _{-3**}
Pv-aCO ₂ (kPa)	0.8	0.7	0.7
H ⁺ _a (mmol/l)	44.7 ⁺ / _{-2.5}	48.6 ⁺ / _{-2.4}	48.9 ⁺ / _{-2.4}
H ⁺ _v (mmol/l)	49.4 ⁺ / _{-2.5}	51.6 ⁺ / _{-2.4}	50.2 ⁺ / _{-2.6}
HCO _{3a} (mmol/l)	21.6 ⁺ / _{-1.5}	20.9 ⁺ / _{-1.5}	20.6 ⁺ / _{-1.6}
HCO _{3v} (mmol/l)	21 ⁺ / _{-1.3}	20.3 ⁺ / _{-1.3}	20.7 ⁺ / _{-1.2}
PaCO ₂ (kPa)	4.7 ⁺ / _{-0.2}	4.9 ⁺ / _{-0.1}	4.9 ⁺ / _{-0.2}
PvCO ₂ (kPa)	5.5 ⁺ / _{-0.2}	5.6 ⁺ / _{-0.2}	5.6 ⁺ / _{-0.1}
XL (mmol/l)	6.4 ⁺ / _{-1.0}	6.4 ⁺ / _{-1.1}	5.9 ⁺ / _{-1.0}
L (mmol/l)	1.9 ⁺ / _{-0.35}	2.1 ⁺ / _{-0.38}	2.0 ⁺ / _{-0.3}

*p < 0.01; **p < 0.001.

CARDIAC INDEX VS. $v\text{-aPCO}_2$

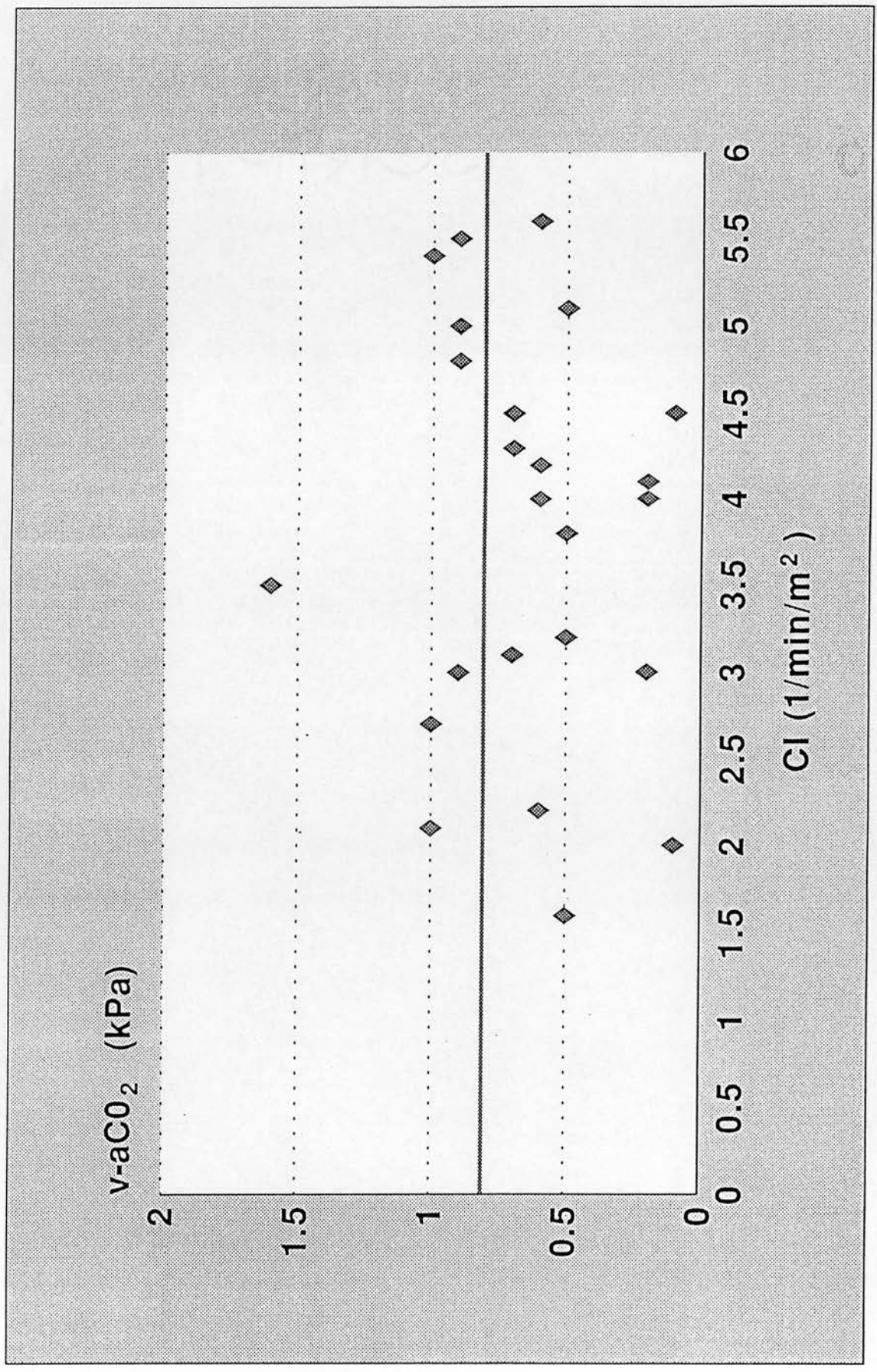


Figure 26

In contrast to studies of patients with low flow shock or cardiac arrest we have failed to demonstrate significant differences in acid-base status between arterial and mixed venous blood. This finding is similar to that of Wendon and colleagues in patients with fulminant hepatic failure (Wendon 1991). However, unlike that study, we failed to demonstrate global increases in VO_2 with increased DO_2 . As we have previously commented, this may reflect the heterogeneity of critically ill patients in terms of their response to a pathophysiological stimulus (in this case sepsis), in the temporal relationships of study and illness, and in the individual's response to therapy.

Several groups have demonstrated venous hypercarbia and a raised P(v-a)CO_2 in human septic shock, but only in those patients with a cardiac output significantly lower than those without venous hypercarbia (Mecher 1990, Bakker 1992). Just as the interpretation of hyperlactataemia may be confounded by multiple factors in addition to tissue anaerobiosis in septic shock, so the interpretation of changes in P(v-a)CO_2 in sepsis is complicated by the effects of impaired myocardial performance, hypermetabolism with increased CO_2 production, buffering of lactic acid and abnormal CO_2 excretion. It appears that there is a fundamental interplay between the circulatory and ventilatory mechanisms in determining the PCO_2 in arterial and mixed

venous blood in states of acute cardio-respiratory failure. Venous hypercarbia results from a combination of factors including increased CO_2 production by the tissues (both as a result of buffering and of ischaemia), increased uptake of CO_2 into capillary blood and abnormal pulmonary blood flow causing impaired CO_2 excretion.

As mentioned in other chapters, the control of minute ventilation is fundamental to the unravelling of the mechanisms of tissue hypoxia and hypercarbia in the unstable situation of acute cardio-respiratory failure. In studies where mechanical ventilation has been used to control minute ventilation, it has been shown that P(v-a)CO_2 increases as cardiac output falls. Our finding that the grouped P(v-a)CO_2 gradient is normal in human septic shock patients who are intubated and mechanically ventilated is in keeping with these other studies. However scrutiny of the relationship between cardiac output and P(v-a)CO_2 in individuals shows that there is no clear relationship between cardiac output and P(v-a)CO_2 difference in this study.

In conclusion, we have demonstrated no increase in venous PCO_2 or P(v-a)CO_2 difference in a group of patients with septic shock. In addition, levels of excess lactate were calculated but showed no benefit compared to lactate concentrations in predicting delivery dependence of DO_2 on VO_2 . None of these markers can be recommended for routine use in this group of

patients. Further work is required to define their place in clinical monitoring.

9.1. Introduction

The studies detailed in this thesis cover a range of aspects important to intensive care treatment. As with much previous research, many questions have been raised in the course of the studies, and further investigation will be of interest in many of the areas discussed.

9.2. Shock and oxygen transport

As more studies showing the importance of high DO_2 in septic shock and critically ill surgical patients have been published, it has become routine clinical practice in many centres to use measurement of oxygen transport to guide therapy in these conditions. However, the effects of vasoactive drugs on individual organ blood flow and metabolism requires to be addressed. There are few clinically applicable techniques available which would allow direct monitoring of this at present, and efforts should be directed at this. The use of gastric intra-mucosal pH measurement as a guide to splanchnic perfusion has been advocated, and we have assessed the effects on this of noradrenaline therapy in septic shock (submitted 1995).

Although preliminary work has highlighted the importance of SvO_2 measurement in low flow states such as cardiogenic shock, there are no large clinical studies of its use as

part of a management protocol aimed at reversing hypotension and critical tissue hypoperfusion simultaneously. The findings of such an investigation would have significant implications for the management of acute myocardial infarction and low flow shock.

9.3. Lactate and critical illness

The place of lactate measurement remains ill-defined. If the concentration is very high, it is useful. However, if the concentration is borderline high or 'normal' it may be of little prognostic relevance, either way. This is probably for one of two reasons. Firstly, certain treatments which reduce oxygen requirements such as paralysis, can improve the oxygen/supply demand balance. In addition while certain organs are net producers of lactate others are utilising it, and in order for ABL to rise these mechanisms must be severely affected. It will be of interest to examine individual organ and tissue lactate kinetics.

It may be necessary to redefine levels of significant hyperlactataemia in different, well defined disease states.

The routine use of intra-venous sodium bicarbonate as a buffer agent in the treatment of hypoxic lactic acidosis has been shown to have no benefit in whole body or intra-cellular terms (Kette 1990, Arieff 1991), and in many situations has been shown to be detrimental (Graf 1985, Bersin 1989, Ritter 1990). Despite initial promise

(Stacpoole 1983), studies of dichloroacetate (a stimulator of lactate metabolism by enhancing the effect of pyruvate dehydrogenase) have failed to show any clinical improvement (Stacpoole 1988, Stacpoole 1992). It would be of considerable interest to study these agents in hypoxic lactic acidosis, combining their use with full invasive monitoring, cardiorespiratory optimisation, and the use of mechanical ventilation to compensate for any excess CO₂ production.

Another interesting agent undergoing trials at present is carbicarb. This equimolar compound of sodium carbonate and sodium bicarbonate elevates blood pH with little increase in PCO₂ compared to sodium bicarbonate (Sun 1987, Bersin 1988). As yet, only preliminary data are available.

9.4. Altering the oxygen supply/demand balance

Although theoretical advantages might accrue from the use of procedures to limit oxygen requirements in critical illness, eg hypothermia, muscle relaxation, sedation, clinical studies demonstrating benefit still require to be carried out.

9.5. Immunomodulation and mediator blockade

Current thinking regarding the use of immunomodulation is influenced to some extent by the ability to measure certain mediators, and more so by the commercial production of a variety of mediator and receptor blockers.

Many authorities have suggested that the use of a 'mediator blocking cocktail' may improve outcome, particularly in sepsis and ARDS. The introduction of these treatments is complicated by the difficulty we face in assessing at what pathophysiological stage the individual is, and in determining which mediators have detrimental rather than beneficial effects. The place of well-tried, relatively inexpensive agents such as aprotinin requires to be defined in clinical practice.

9.6. **Summary**

The monitoring of shock and critical illness has evolved rapidly in the last 25 years, no more so than in the late 1980s and early 1990s. Following the pioneering work of Shoemaker, many groups of investigators and clinicians have studied and utilised oxygen transport in a more cohesive manner than heretofore. The use of these measurements to guide resuscitation has become routine in many places, although certain groups still advocate the utility of isolated lactate measurements. Until individual organ and tissue blood flow, oxygen transport and lactate metabolism are clinically measurable, global measurements provide us with the most accurate guide to the adequacy of the cardiorespiratory system, and should probably be used earlier and more widely than is currently the case. These suggestions are not novel (Gurd 1966, Talley 1969). However until the realisation of new treatments or

strategies the timely provision of adequate oxygenation, volume resuscitation and appropriate cardiorespiratory support to the critically ill should prevent the development of multiple organ failure, hopefully with improved survival the logical reward.

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The relationship of blood lactate concentrations, oxygen delivery and oxygen consumption in septic shock and the adult respiratory distress syndrome

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Summary

Tissue hypoxia is thought to be pivotal to the development of multiple organ failure, but cannot be measured directly in clinical practice. We assessed the relationship between initial arterial blood lactate concentrations and the presence of the phenomenon of delivery-dependent oxygen consumption, both of which may indicate tissue hypoxia. Twenty-three critically ill patients with septic shock and adult respiratory distress syndrome were studied prospectively and allocated to one of two groups according to blood lactate concentrations. In group 1, blood lactate concentration was less than the level widely accepted as significant (2 mmol.l^{-1}); in group 2, the concentration exceeded 2 mmol.l^{-1} . In both groups, resuscitation with colloid, blood and vasoactive drugs resulted in significant increases in oxygen delivery; in group 1 ($n = 13$), mean (SEM) oxygen delivery increased from 484 (36) to 730 (44) $\text{ml.min}^{-1}.\text{m}^{-2}$ ($p < 0.005$) and in group 2 ($n = 10$) from 550 (54) to 780 (54) $\text{ml.min}^{-1}.\text{m}^{-2}$ ($p < 0.05$). In neither group was there a significant change in oxygen consumption. However, there were individuals in both groups who exhibited pathological delivery dependence. This suggests that the absence of hyperlactataemia does not preclude delivery dependence of oxygen consumption with the attendant potential for tissue hypoxia.

Key words

Shock; septic.

Lungs; respiratory distress syndrome.

Metabolism; lactate.

Oxygen; consumption.

Elevated arterial blood lactate concentrations have long been recognised as being a consequence of tissue hypoxia [1, 2], and of having significant prognostic importance [3-5]. However, there are many causes of hyperlactataemia other than tissue hypoxia; these include hyperglycaemia, hypocapnia, toxins, liver failure and some malignancies [1, 6]. It is generally accepted that hyperlactataemia in patients with acute cardiorespiratory failure results from a combination of overproduction of lactate in hypoxic tissues and of reduced clearance and metabolism [6]. The liver and kidneys may become net producers of lactate in shock [7]. The cardiorespiratory findings in septic shock and adult respiratory distress syndrome (ARDS) may include increased cardiac output and oxygen delivery. Despite the presence of an apparently adequate oxygen delivery there is an impediment to normal tissue oxygen utilisation which has long been recognised

but is still not fully understood [8, 9]. It has been shown that, by increasing oxygen delivery in these patients using fluids, blood or vasoactive drugs, oxygen consumption ($\dot{V}\text{O}_2$) may increase even when oxygen delivery exceeds the $330 \text{ ml.min}^{-1}.\text{m}^{-2}$ below which such a relationship is thought to be physiological [10-13]. Delivery-dependent oxygen consumption at these levels is a pathological state which is in stark contrast to the norm. Recent work has suggested that elevated blood lactate concentrations characterise those patients with shock or ARDS who exhibit delivery-dependent $\dot{V}\text{O}_2$ [14, 15] although we have previously shown that hyperlactataemia is not a universal finding in shock [16]. We have therefore re-examined the association between blood lactate concentration and delivery dependence in the critically ill. During resuscitation of 23 critically ill patients with septic shock and ARDS, serial cardiorespiratory profiles with concurrent blood lactate

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concentrations were obtained and the influence of these on the relationship between oxygen delivery and consumption studied.

Methods

We studied 23 patients who required intensive care, invasive haemodynamic monitoring and mechanical ventilation for the management of septic shock ($n = 21$) and ARDS ($n = 2$). The study was reviewed and approved by the local ethics committees. Septic shock was defined as mean arterial pressure (MAP) < 70 mmHg with oliguria, despite controlled volume expansion to an optimal pulmonary artery occlusion pressure (PAOP), in the presence of positive bacteriology. ARDS was defined as severe hypoxaemia which required mechanical ventilation with $P_{iO_2} > 0.5$ to maintain $P_{aO_2} > 10$ kPa; diffuse infiltrates on chest X ray; shunt ratio $> 30\%$; PAOP < 18 mmHg; and the presence of a known risk factor.

All patients were sedated with continuous infusions of papaveretum $3-5$ mg.h $^{-1}$ and midazolam $1-3$ mg.h $^{-1}$, and the muscles were paralysed with atracurium. No changes in rates of infusion of these drugs were made during the study period, and the only adjustments to ventilator settings were of P_{iO_2} . All patients were studied during the first 6 h of resuscitation following admission to the intensive care unit. Femoral arterial and thermodilution pulmonary artery flotation catheters (PAFC: Swan-Ganz, Baxter/Edwards, Irvine, CA) were used in all patients for measurement of mean arterial pressure (MAP), mean pulmonary artery pressure (PAM), end-expiratory pulmonary artery balloon occluded (wedge) pressure, and mean right atrial pressure (RAP), all zeroed to the phlebostatic axis. Cardiac output was determined by thermodilution in triplicate using 10 ml dextrose 5% at a temperature of $< 10^\circ\text{C}$. Continuous ST segment analysis was performed using, and heart rate measured from, 5 lead ECG monitoring (7200 series bedside monitors, Marquette Electronics, Milwaukee, WI). Samples of mixed venous and arterial blood were taken for blood gas analysis within 1 min of the last cardiac output measurement. Haemoglobin concentration and mixed venous and arterial oxyhaemoglobin saturations were measured using an oximeter (Ciba Corning). The oxygen content of arterial (CaO_2) and mixed venous ($\text{C}\bar{\text{v}}\text{O}_2$) blood, and oxygen delivery and consumption, were calculated using standard formulae. By convention, cardiac output is indexed for body surface area, and we calculated oxygen delivery as the product of CaO_2 and cardiac index (CI). Oxygen consumption (also indexed to body surface area) was calculated using the inverse Fick relationship: $\dot{V}\text{O}_2 = \text{cardiac index} \times \text{arteriovenous oxygen content difference}$.

At the time of arterial sampling, blood was taken for lactate measurement. A volume of 1.5 ml of blood was placed into preweighed glass tubes containing 5 ml of cold (4°C) 5% perchloric acid, immediately refrigerated and subsequently analysed. Lactate concentration was measured using a Cobas Bio (Roche) centrifugal analyser, monitoring the rate of reduction of NAD to NADH $^+$ fluorimetrically at an excitation wavelength of 340 nm in 0.5 M glycine buffer (pH 9.6) in the presence of 0.2 M hydrazine hydrate and lactate dehydrogenase. Lactate standards from 50–1200 mmol.l $^{-1}$ were used. Whole blood lactate concentration was then calculated after correcting

for dilution of the blood sample with 5% perchloric acid. The assay had a sensitivity of 0.05 mmol.l $^{-1}$ and a coefficient of variation of 5.8–7.9% depending on the concentration range. We have previously validated the use of arterial rather than mixed venous samples for lactate measurement [17].

Following baseline measurements, further controlled volume expansion was performed in all patients after comparison of the haemodynamic profile with previously described therapeutic goals: MAP > 80 mmHg, CI > 4.5 l.min $^{-1}$.m $^{-2}$ and oxygen delivery 600 ml.min $^{-1}$.m $^{-2}$ [18, 19]. Colloid and blood were used, depending on haemoglobin concentration. After volume expansion, all patients received combinations of vasoactive drugs (Table 1), depending on the haemodynamic profile, in doses titrated against the observed haemodynamic effects with the intention of reaching the defined therapeutic goals. The baseline variables were compared to the variables associated with maximal oxygen delivery within the first 6 h of resuscitation. Patients were allocated into one of two groups on the basis of the initial blood lactate concentration (group 1, lactate < 2 mmol.l $^{-1}$; group 2, lactate > 2 mmol.l $^{-1}$). This threshold for significant hyperlactataemia is that described by several investigators [2, 20].

Statistical analysis

All results are expressed as mean (SEM). Baseline data from the two groups of patients were compared by means of the Wilcoxon rank sum test, and the paired data obtained before and after resuscitation were compared with the Wilcoxon signed rank test. Differences were considered significant at $p < 0.05$.

Results

The 23 patients (11 female) were each studied on one occasion. The mean age was 55 years (range 36–81). Clinical data, including admission APACHE II scores, are shown in Table 1, and haemodynamic and oxygen transport data are detailed in Tables 2 and 3. Baseline measurements were compared in the two groups. Heart rate, oxygen delivery and lactate concentrations were significantly higher in group 2.

Following resuscitation, there were significant comparable increases in cardiac index, mixed venous oxygen saturation and oxygen delivery, and decreased oxygen extraction, in both groups. There was a significant increase in MAP ($p < 0.05$) only in group 1. There were no significant changes in mean $\dot{V}\text{O}_2$ or lactate concentration in either group, although there were marked individual changes in $\dot{V}\text{O}_2$ in some patients in both groups (Figs 1–4). There was one death during the study period (patient 16). In group 1, six of 13 patients survived to leave hospital; three out of 10 survived in group 2.

Discussion

It has been recognised for many years that inefficient utilisation of oxygen is a fundamental defect in septic shock [8]. This finding has been confirmed recently, and a similar situation has been described in ARDS [12, 19]. The pathophysiological abnormality is characterised by depen-

Table 1. Clinical details: group 1.

Patient	Age	Sex	Primary diagnosis	APACHE II	Vasoactive drug ($\mu\text{g.kg}^{-1}.\text{min}^{-1}$)	Outcome
1.	58	F	Pneumonia β -haemolytic streptococcal SS	27	NOR 0.05 DOP 3 DOB 15	S
2.	63	F	Pneumonia Cardiorespiratory arrest Septic shock	15	DOB 10	S
3.	68	M	Faecal peritonitis ARDS	22	DOB 3	S
4.	38	F	Guillain Barré SS, ARDS	12	NOR 0.05 ADR 0.06	NS
5.	73	M	Acute pancreatitis Perforated colon SS, ARDS	21	DOB 30 NOR 0.4	NS
6.	54	F	Pneumococcal pneumonia SS, ARDS	10	NOR 0.07	NS
7.	72	M	SS	28	DOB 15 NOR 0.28	NS
8.	57	M	Perforated diverticulum ARDS	3	DOB 5	S
9.	80	M	Subphrenic collection post- gastrectomy, SS, ARDS	25	DOB 4 NOR 0.12	NS
10.	52	F	Pneumococcal pneumonia ARDS	21	DOP 2 NOR 0.08	S
11.	65	F	SS, ARDS	21	DOB 5	NS
12.	64	F	SS (enterococci), ARF	25	DOB 15	NS
13.	45	M	Necrotising fasciitis, SS, ARDS	16	NOR 0.05	S

Clinical details: group 2.

14.	81	F	Faecal peritonitis Respiratory arrest, SS	18	ADR 0.04	NS
15.	59	F	Empyema, SS (β -haemolytic streptococci) Squamous carcinoma of lung	27	DOB 5 ADR 0.06	NS
16.	63	M	SS (β -haemolytic streptococci) Pneumonia Respiratory arrest	25	DOB 10 NOR 0.03	NS
17.	65	F	Necrotising fasciitis SS	20	DOB 12	S
18.	73	M	SS (coliforms) Indwelling urinary catheter	31	ADR 0.4 NOR 0.9	NS
19.	75	M	Faecal peritonitis Infarcted colon, SS	18	NOR 0.14	NS
20.	58	M	Ulcerative colitis Infarcted small bowel	21	NOR 2	NS
21.	80	M	Pneumonia SS	33	NOR 0.04 ADR 0.06	NS
22.	42	F	Post-colectomy SS	15	DOB 5 NOR 0.3	S
23.	70	M	Post-cystectomy (carcinoma bladder) SS	35	ADR 0.15 NOR 0.2	S

SS, septic shock; ARDS, adult respiratory distress syndrome; ARF, acute renal failure; DOP, dopamine; DOB, dobutamine; ADR, adrenaline; NOR, noradrenaline; S, survivor; NS, nonsurvivor.

dence of $\dot{V}O_2$ on oxygen delivery at levels of delivery which are well above the previously described critical level [13]. Oxygen consumption can thus be increased by increasing delivery, suggesting that tissue perfusion is inadequate. The mechanisms responsible for this phenomenon are not completely clear but probably involve a combination of factors including maldistribution of tissue blood flow due to

vaso-deregulation [21], an increase in capillary-to-cell diffusion distance caused by the interstitial oedema associated with capillary leak [22] and dysfunction of organelles as a result of the mediators and toxic elements generated and released in the inflammatory responses of sepsis and ARDS [23]. In addition, the demand for oxygen may be increased by fever, shivering or rigors [24]. Many investiga-

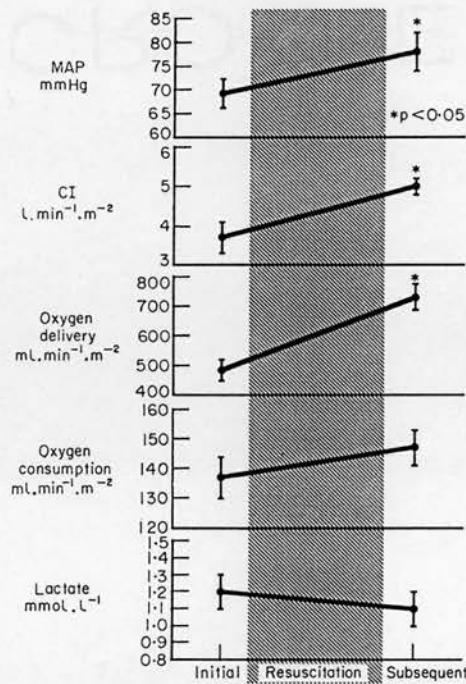


Fig. 1. Haemodynamic, oxygen transport and blood lactate changes during resuscitation in group 1 (initial blood lactate < 2 mmol.l⁻¹). MAP, mean arterial pressure; CI, cardiac index.

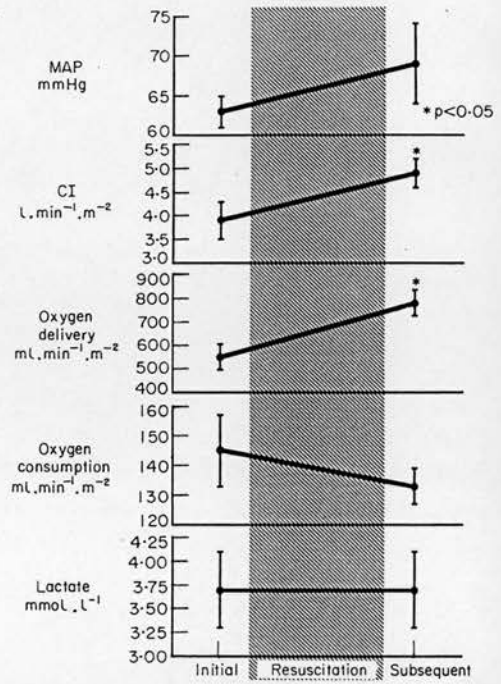


Fig. 2. Haemodynamic, oxygen transport and blood lactate changes during resuscitation in group 2 (initial blood lactate > 2 mmol.l⁻¹). MAP, mean arterial pressure; CI, cardiac index.

Table 2. Haemodynamic variables at baseline and after initial resuscitation. Data are presented as mean (SEM).

	Group 1 (Lactate < 2 mmol.l ⁻¹) n = 13		Group 2 (Lactate > 2 mmol.l ⁻¹) n = 10	
	Baseline	Resuscitation	Baseline	Resuscitation
HR (beat.min ⁻¹)	109 (6)	117 (5)	128 (5)†	127 (4)
MAP (mmHg)	70 (3)	78 (4)*	63 (2)	69 (5)
PAOP (mmHg)	13 (2)	15 (1)	13 (2)	13 (1)
CI (l.min ⁻¹ .m ⁻²)	3.7 (0.4)	5.0 (0.2)*	3.9 (0.4)	4.9 (0.3)*

MAP, mean arterial pressure; HR, heart rate; PAOP, pulmonary artery occlusion (wedge) pressure; CI, cardiac index; difference from baseline: *p < 0.05; between group comparison: †p < 0.05.

Table 3. Lactate and oxygen transport variables at baseline and after initial resuscitation. Data are presented as mean (SEM).

	Group 1 (Lactate < 2 mmol.l ⁻¹ ; n = 13)		Group 2 (Lactate > 2 mmol.l ⁻¹ ; n = 10)	
	Baseline	Resuscitation	Baseline	Resuscitation
Oxygen delivery (ml.min ⁻¹ .m ⁻²)	484 (36)	730 (44)**	549 (54)†	779 (54)*
Oxygen consumption (ml.min ⁻¹ .m ⁻²)	137 (7)	147 (6)	145 (12)	133 (6)
OER (%)	29 (2)	21 (1)*	28 (3)	18 (2)*
SvO ₂	69 (2)	77 (1)*	71 (3)	80 (2)*
Qs/Q _t (%)	28 (3)	32 (3)	27 (3)	34 (3)
Lactate (mmol.l ⁻¹)	1.2 (0.1)	1.1 (0.1)	3.7 (0.4)†	3.7 (0.4)

OER, oxygen extraction ratio; SvO₂, mixed venous oxyhaemoglobin saturation; Qs/Q_t, pulmonary shunt fraction; difference from baseline: *p < 0.05, **p < 0.005; between group comparison: †p < 0.05.

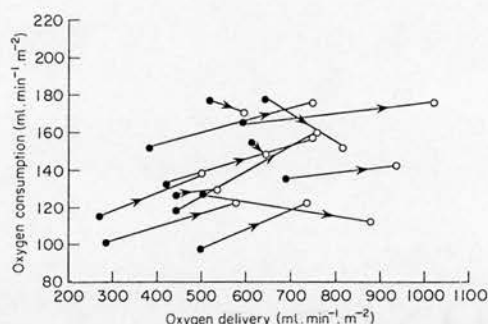


Fig. 3. Oxygen delivery and oxygen consumption changes during resuscitation in individual patients in group 1.

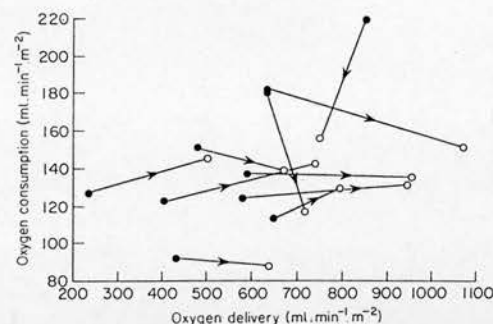


Fig. 4. Oxygen delivery and oxygen consumption changes during resuscitation in individual patients in group 2.

tors have confirmed this phenomenon [9–12, 14, 15]. In some of these studies, it has been suggested that $\dot{V}O_2$ rises significantly only in those individuals with severe tissue hypoxia, as evidenced by critically elevated blood lactate concentrations. This is in accordance with the study of Duff *et al.* [8] who showed that their septic patients with the highest lactate values had the lowest $\dot{V}O_2$ levels. There is, however, some disagreement about the value of hyperlactataemia as a predictor of supply-dependency in sepsis and ARDS. Vincent *et al.* [14] have used low-dose dobutamine ($5 \mu\text{g.kg}^{-1}.\text{min}^{-1}$) to perform a short oxygen flux test in an attempt to disclose supply dependency of $\dot{V}O_2$ in stable patients with heart failure or sepsis. Dobutamine resulted in significant increases in CI and oxygen delivery but $\dot{V}O_2$ increased only in those patients with elevated blood lactate concentrations. Gilbert *et al.* [25] also demonstrated increased $\dot{V}O_2$ with increased oxygen delivery in response to infused catecholamines in septic patients with elevated lactate concentrations. However, previous work has suggested that the relationship between tissue hypoxia and hyperlactataemia in shock is much less clear-cut than may have been suggested [16]. Indeed, there is a subgroup of patients with the clinical and haemodynamic features of shock who have normal lactate concentrations.

We undertook the present study in the light of these controversies and because of the possibility that unrecognised tissue hypoxia may be present even in the absence of a critically elevated lactate concentration. We chose to include unstable patients during initial resuscitation in contrast to previous investigators who studied relatively stable, resuscitated patients. We were interested particularly in the relationship between oxygen delivery and consumption in patients without hyperlactataemia over this initial period. The timespan of study (up to 6 h, mean 3.2) was similar to that of previous work [15], although it might be suggested that the overall oxygen demand could change substantially over the study period described. This is a valid point, although work with continuous monitoring of mixed venous oxygen saturation and continuous on-line $\dot{V}O_2$ measurement shows that oxygen demand can change significantly from minute to minute in otherwise apparently stable patients [24, 26]. Unlike other investigators, we have rigorously standardised other factors which may affect $\dot{V}O_2$ or lactate independently. Patients with hyperglycaemia and liver failure were excluded. The contribution of work of breathing to $\dot{V}O_2$ and lactate production has been shown to

be considerable [27], and so all patients in our study were sedated and their lungs ventilated mechanically.

We allocated our patients to groups on the basis of blood lactate concentration rather than the type of resuscitation therapy received. Previous studies have concentrated on the use of either volume or vasoactive drugs. In both groups, significant increases of CI and oxygen delivery were achieved, but in the hyperlactataemic patients the increase in blood pressure achieved was not significant despite the enthusiastic administration of fluids and vasopressors. We have suggested previously that hyperlactataemia will be cleared reliably in the majority of shock patients only when flow, oxygen delivery and blood pressure are increased concurrently [16]. This hypothesis is supported by the results of those studies in which CI and oxygen delivery have been increased with no accompanying improvement in MAP from low levels [3]. In patients who remained hypotensive despite significantly increased blood flow, lactate concentrations remained high or increased further, with 100% mortality.

In our study, the inability to improve flow and MAP together in patients 14, 16, 18, 19 and 20 was associated with increasing lactate concentrations and death. The influence on the response to therapy of the underlying disease process, the inability to eradicate sepsis and pre-existing severe cardiorespiratory dysfunction have all been suggested as potential reasons for the poor outcome in these patients.

Examination of the relationship between oxygen delivery and consumption in individual patients reveals another tantalising discrepancy. The pooling of data for statistical analysis obscures individual idiosyncratic responses of $\dot{V}O_2$ to oxygen delivery. In particular, $\dot{V}O_2$ increased by between 17 and 35% in six patients with normal lactate concentrations. There were no increases in lactate, and this suggests that the increase in $\dot{V}O_2$ was not demand-led by a catecholamine-induced rise in metabolism. It is possible that unrecognised tissue hypoxia is present in critically ill patients even in the absence of critically elevated blood lactate. Since the production of hyperlactataemia in experimental models often requires combinations of severe anaemia, hypoxaemia, reduced cardiac output and profound hypotension, the finding of elevated lactate concentrations in clinical situations is likely to indicate an advanced degree of tissue hypoxia. The finding of normal lactate concentrations in patients with acute cardiorespiratory failure due to

sepsis and ARDS may not preclude the presence of a tissue oxygen debt. As blood lactate appears to be a fairly insensitive marker of tissue hypoxia, we are currently re-evaluating excess lactate, a potentially more sensitive guide [1]. Justifiable concerns on the effects of vasoconstrictors on regional blood flow and hence tissue oxygenation have been voiced, and recent work has documented the unpredictability of splanchnic blood flow responses, highlighting the need to withdraw vasoconstrictors as early as possible [28].

Basic therapy in these patients should therefore be directed to improving oxygen delivery and blood pressure concurrently, whilst attempting to correct or remove the underlying cause. The levels of oxygen delivery and MAP required in any individual situation remain very difficult to determine although a randomised study has shown an improvement in survival when supranormal oxygen delivery is achieved [29]. It appears clear that the finding of a normal blood lactate concentration should not encourage complacency, since this does not exclude supply dependency. Further research into the effects of independent factors such as sedation, paralysis and mechanical ventilation on the relationship between oxygen delivery and consumption is required to further unravel the complex pathophysiology.

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Cardiorespiratory and Metabolic Studies in Shock and Critical Illness

1. In all of the clinical studies appropriate Local Medical Ethics Committee approval was sought and obtained.
2. In the animal studies a Home Office Project Licence was obtained for the work performed. In addition, Dr Allan D. Cumming and myself both obtained Personal Licences for Procedures on Living Animals. Regular Home Office visits took place over the course of the experiments.
3. Page 61: the normal range for lactate on the analyser in ICU at the University Hospital of South Manchester is 0.6 to 1.2 mmol/l, and that in Edinburgh is 0.4 to 1.2 mmol/l.
4. Page 74: It has been demonstrated that B-agonists, in particular adrenaline, can increase blood lactate concentrations by a direct metabolic action. The exact nature of this effect is unclear but probably involves an effect on lactate dehydrogenase, NADH or on prevailing glucose concentrations. Thus, it should be noted that an increase in blood lactate concentration in the presence of increased circulating concentrations of adrenaline or noradrenaline (endogenous or exogenous) may be due to a metabolic rather than a hypoxic mechanism.
5. Page 103: Sedation level medians: Time zero 2.5, 30 mins 5, 1 hour 5.25, 3 hours 5.25, 6 hours 5.25.
6. Page 129: Randomisation of subjects in the Protocol Study was by means of pre-prepared envelopes. These were supplied from the manufacturer of the aprotinin, along with the placebo bottles of vehicle. The investigators were blinded to the contents of the vials being administered, the bottle to be used being determined by the number obtained from the envelope.
7. Page 155: It should be made clear that some results from the patients used for this study had already been reported in previous chapters. This study should be regarded as a sub-group analysis of the earlier studies.
8. Page 156: Lactate measurement in relation to DO_2/VO_2 changes: it was hoped that lactate or excess lactate would prove a marker for tissue hypoxia as evidenced by delivery dependence of VO_2 on DO_2 . In Chapter 4 it was shown that this is not the case for lactate alone. In Chapter 8 a small number of patients in whom excess lactate was calculated were examined to see if this relationship were any more predictive. In these individuals elevated excess lactate did not have any clear relationship to delivery dependent VO_2 . In this small group no increased sensitivity of excess lactate concentrations over lactate alone could be demonstrated.

Hemodynamic, renal, and hormonal actions of aprotinin in an ovine model of septic shock

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Background and Methods: Previous studies documented activation of protease enzymes such as the plasma kallikrein-kinin system in endotoxemia and sepsis, both in experimental animals and in patients. We investigated the actions of aprotinin (a protease inhibitor that binds to plasma kallikrein) on systemic hemodynamics and renal function, in an ovine model of septic shock. Aprotinin was infused intravenously in high dosage (1×10^6 kallikrein inhibitor units [KIU] loading, 200,000 KIU/hr), commencing 30 mins after surgical induction of sepsis (cecal ligation and puncture).

Results: In the control group ($n = 6$), there were significant decreases with time in BP and systemic vascular resistance, an increase in pulmonary artery pressure, reductions in creatinine clearance and sodium excretion, and an increase in plasma renin activity. In aprotinin-treated animals ($n = 6$), none of these changes occurred. There were significant between-group differences (controls vs. treatment) for mean arterial pressure, pulmonary artery pressure, and plasma renin activity.

Conclusions: In this large animal model of septic shock, which reproduces the important features of clinical sepsis, treatment with aprotinin after the initiation of sepsis appears beneficial in relation to systemic hemodynamics, renal function, and hormonal stimulation, with no evidence of adverse effects. (Crit Care Med 1992; 20:1134-1139)

KEY WORDS: septic shock; aprotinin; renal function; acute renal failure; kallikrein; kinin; renin; protease inhibitors; endotoxins; hemodynamics

Among the mediator systems known to be activated in endotoxemia and sepsis are a number of protease enzymes, activation of which is known to be associated with important biological effects (1). For example, there is an association between endotoxemia and sepsis, and activation of the plasma kallikrein-kinin system. In septic shock, Colman and Wong (1) and others (2, 3) described reduced plasma concentrations of plasma prekallikrein, increased "kallikrein-like activity," and decreased kallikrein-inhibitory activity, probably as a result of endotoxin-induced activation of the Hageman factor. Kinins could mediate several important features of septic shock; in particular, kinins are potent systemic vasodilator peptides, but constrict the pulmonary circulation in most species (4). They cause increased capillary permeability and stimulate release of arachidonic acid from cell membranes, leading to increased prostaglandin and thromboxane synthesis (4). However, it is uncertain whether the reduced plasma prekallikrein in sepsis is wholly due to kallikrein-kinin system activation, or, in part, reflects reduced prekallikrein synthesis (5). It is also unclear whether kallikrein-kinin activation is directly involved in the pathogenesis of septic shock. Previous studies (6-8) of the response to experimental endotoxin infusion failed to support this hypothesis, although because of the lack of potent and specific kallikrein-kinin antagonists, direct evidence is lacking. Aprotinin (Trasylol, Bayer, Wuppertal, FRG) is a serine protease inhibitor with some kallikrein-inhibitory activity (9). The affinity of aprotinin for kallikrein is, however, less than that affinity for some other proteases (9), and previous studies (10) of this agent used doses of aprotinin that are now recognized to inhibit plasma kallikrein poorly, if at all. We (11) studied the effect of aprotinin, at a dose known to achieve maximal plasma kallikrein inhibition, in a large animal (ovine) model of intraperitoneal and systemic sepsis that reproduces many of the important features of clinical septic shock.

Sepsis and acute renal failure are frequently associated, and $\leq 50\%$ of cases of acute renal failure are caused by septicemia (12). The pathogenesis of this syndrome is poorly understood, but recent studies (13, 14) suggested that the systemic arterial vasodilation that occurs in early sepsis may be the principal stimulus

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causing the kidney to retain solutes and water, leading to functional renal failure associated with reduced glomerular filtration and sodium retention. Our own studies (11, 14) suggested that this renal response may reflect renin-angiotensin activation, together with reduced activity of the intrarenal tissue kallikrein-kinin system, which normally acts to preserve renal function during hypoperfusion. Therefore, it was important to discover whether aprotinin treatment, which could further reduce renal kallikrein activity, adversely affected renal function in intraperitoneal and systemic sepsis. The overall hypothesis of the study was that aprotinin therapy would prevent or ameliorate hypotension and systemic vasodilation in sepsis, and that these beneficial actions on the systemic circulation would outweigh any effect of local renal tissue kallikrein inhibition.

MATERIALS AND METHODS

This study was approved under a project license by the Home Office, and conformed to UK Government regulations regarding the care of experimental animals. The technique of surgical induction of peritonitis was modified from that of Wichterman et al. (15), as previously described (11, 14). Twelve healthy sheep, aged 12 to 18 months and weighing 40 to 50 kg, required general anesthesia and cannulation of the common carotid artery, and the pulmonary artery via the external jugular vein with a triple-lumen pulmonary artery flotation catheter. The bladder was catheterized per urethra. After recovery from anesthesia, animals were intravenously volume-loaded with 4 L of lactated Ringer's solution over 24 hrs. After control hemodynamic measurements and blood and urine sampling, the animals underwent a second general anesthetic; peritonitis was induced by cecal ligation and puncture. Postoperatively, all animals received 50 mg pethidine iv, and were continued thereafter on an iv infusion of pethidine (50 mg/6 hrs). Intravenous infusion of lactated Ringer's solution (150 mL/hr) continued for the duration of the experiment, and the rate of additional fluid administration was adjusted to maintain pulmonary artery occlusion pressure (PAOP) at baseline values. Hemodynamic measurements were made hourly, and blood and urine collections were made four hourly after induction of sepsis.

Animals were supervised continuously during the study. Any animal seen to be restless, agitated, or showing other evidence of discomfort or distress, despite pethidine infusion, was killed immediately by iv injection of pentobarbital. Animals surviving through 12 hrs were killed as above; an open renal biopsy was taken at the time of death.

Hemodynamic variables measured were: mean arterial pressure, central venous pressure, mean pulmonary artery pressure, PAOP, and thermodilution cardiac output. Cardiac index and systemic vascular resistance index were derived by standard formulas.

In the treatment group ($n=6$), aprotinin was infused intravenously, commencing 30 mins after the completion of surgical induction of peritonitis. A loading dose of 1×10^6 kallikrein inhibitor units was given, followed by 200,000 kallikrein inhibitor units hourly throughout the study. In control animals ($n=6$), the saline vehicle alone was infused at the same rate.

Blood samples were taken from the aortic cannula. Plasma concentrations of creatinine, sodium, and osmolarity values were measured by standard autoanalyzer techniques. Plasma renin activity was measured by radioimmunoassay. Urine volume was recorded. Urine kallikrein concentration was measured by the method of Amundsen et al (16). The assay measured the urine activity against the chromogenic substrate S-2266 (H-D-Val-Leu-Arg-pNA, AB Kabi Diagnostica, Stockholm, Sweden), for which urine kallikrein is highly specific. An aprotinin buffer was added to a sample blank for each sample. A total of 500 μ L of buffer was added to 400 μ L urine and incubated at 37°C for 5 mins; 100 μ L of S-2266 was added and incubated for 30 mins. The reaction was stopped by the addition of 100 μ L 50% acetic acid. The absorbance of each sample was read against its blank at 405 nm. Results were expressed as nkat/L, 1 nkat being the amount of glandular kallikrein that cleaves 0.05 μ mol of substrate/min under the given conditions. This value was calculated as $\text{nkat/L} = 146 \times \text{absorbance}$. Interassay coefficient of variation was 8.2%, and intra-assay coefficient of variation was 4.5%.

Kidney tissue was examined by light microscopy, using standard methods (17). For the purposes of analysis, for each variable, the values included were those values at baseline (presepsis) and observations made at 4 and 8 hrs postoperatively and at the termination of the study (12 hrs postoperatively). Two-way analysis of variance for repeated measures was used to assess the significance of changes with time for each variable in the treatment and the control groups, and the significance of between-group (aprotinin treatment) effects. All statistical procedures were performed using the SPSS-PC statistical package on an IBM 55SX computer. Values for $p < .05$ were considered significant. Results are shown as mean \pm SEM.

RESULTS

As in the studies (11, 14) performed to establish and validate this experimental model, animals developed a

polymicrobial peritonitis and bacteremia. Organisms grown on blood culture included: *Escherichia coli*, *Serratia*, *Enterobacter*, *Pseudomonas*, and *Bacteroides* species. Autopsy showed generalized purulent peritonitis and an inflammatory mass in the right lower quadrant. PAOP was maintained in the range of 10 to 20 mm Hg during the study (mean for controls 14.1 ± 1.6 mm Hg; aprotinin group 13.4 ± 2.2 mm Hg, $p > .05$). There was no clinically important difference in the amount of fluid given in the two groups (controls 4.3 L/12 hrs; aprotinin group 3.9 L/12 hrs, $p > .05$).

Results for systemic hemodynamics and renal function at baseline and during the study are shown in Figures 1 and 2. In the control animals ($n = 6$), there were clinically important decreases with time in BP (Figure 1A) and in systemic vascular resistance index (Figure 1B), an early increase in pulmonary artery pressure (Figure 1C), and reductions in creatinine clearance (Figure 2A) and fractional sodium excretion (Figure 2B). None of these variables altered significantly in the aprotinin-treated animals ($n = 6$). Cardiac index and urine volume did not change significantly with time in either group. There was a statistically significant effect of aprotinin treatment in a two-way analysis of variance for the variables, mean arterial pressure ($p < .05$), and pulmonary artery pressure ($p < .01$).

In the control group, urine kallikrein excretion tended to decrease during sepsis, and there was a significant increase with time in plasma renin activity; these changes were noted in prior studies (14) of this model. Aprotinin treatment was associated with lower urine kallikrein excretion during sepsis, although the difference was not statistically significant. Plasma renin activity did not increase significantly in the aprotinin-treated group, and plasma renin activity was significantly lower in this group at the conclusion of the study (Table 1).

No consistent or significant changes in renal histology were noted in treatment or control groups, in keeping with previous studies. The changes that were observed included: mild tubular dilation, occasional foci of tubular regeneration, and patchy interstitial infiltrate of mononuclear cells. These changes were evenly distributed between treatment and control groups.

DISCUSSION

Studies of pharmacologic intervention in clinical septic shock are complicated by a lack of presepsis baseline parameters, problems in assessing the stage and severity of the shock syndrome, and the multiple treatments required. The experimental model of sepsis

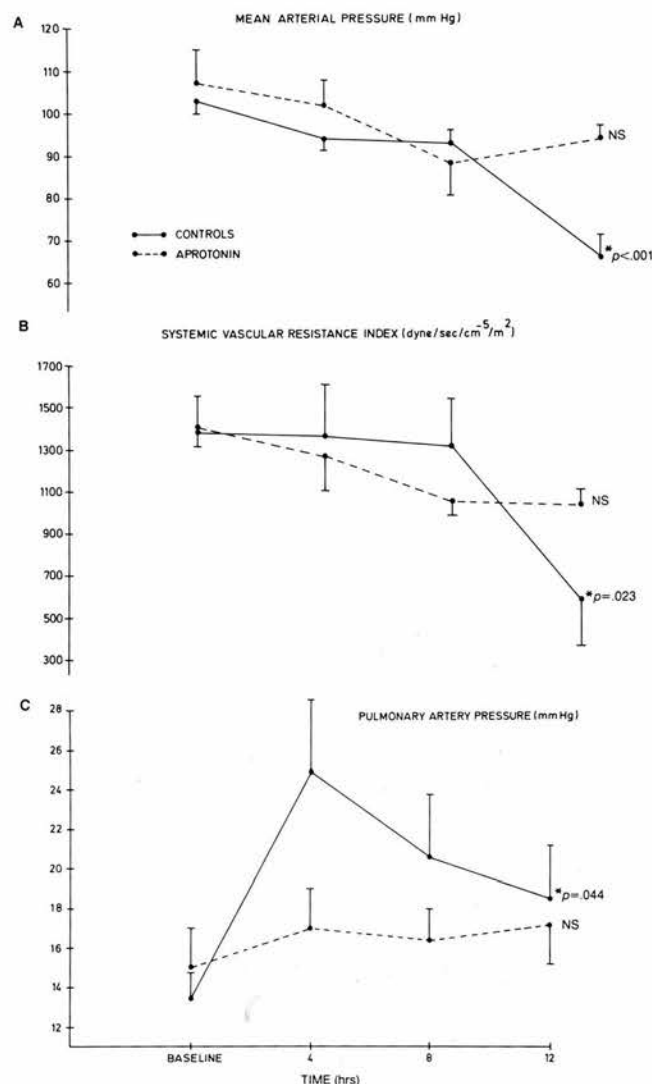


Figure 1. A) Mean arterial pressure (MAP) in control and aprotinin-treated groups; B) systemic vascular resistance index (SVRI) in control and aprotinin-treated groups; C) pulmonary artery (PA) pressure in control and aprotinin-treated groups. All values are mean \pm SEM. NS, nonsignificant. Note the decrease in MAP and SVRI at 12 hrs in the control group only, and the increase in PA pressure at 4 hrs in control group only. Significance values refer to change over time for control and treatment groups.

utilized in this study overcomes these difficulties and differs from most other experimental models of sepsis and endotoxemia in that it reproduces the state of volume-loaded, hyperdynamic, and vasodilated septic shock typically seen in clinical practice (18). The use of an ovine model allows detailed hemodynamic monitoring and provides sufficient blood and urine sample size to permit assessment of renal function and vasoactive hormone systems.

The initial events that trigger systemic vasodilation in sepsis are unclear. However, bacterial endotoxins are potent activators of the plasma "contact systems,"

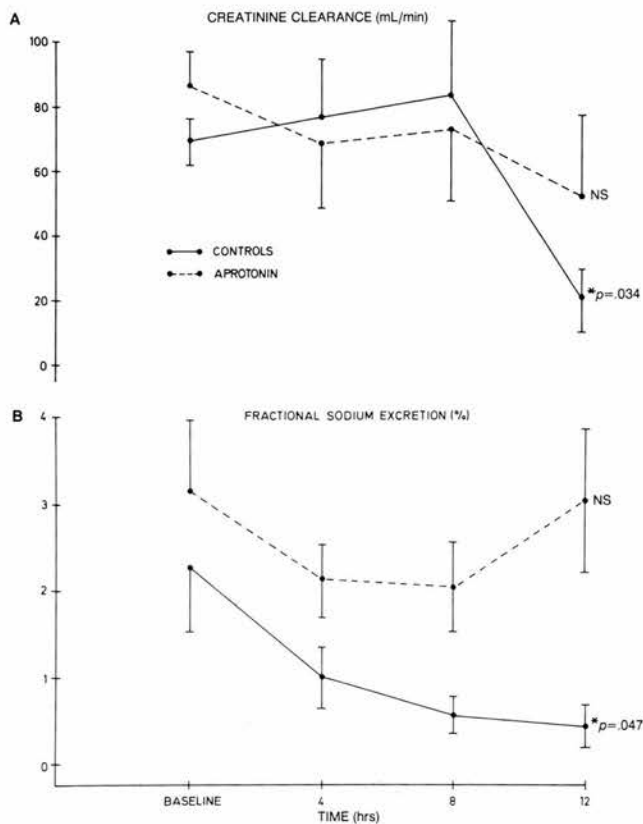


Figure 2. A) Creatinine clearance in control and aprotinin-treated groups; B) fractional sodium excretion in control and aprotinin-treated groups. All values are mean \pm SEM. NS, nonsignificant. Note the decrease in creatinine clearance and fractional sodium excretion at 12 hrs in the control group only. Significance values refer to change over time for control and treatment groups.

through the Hageman factor; these contact systems include the plasma kallikrein-kinin system (5). Plasma kallikrein is a serine protease, generated from an inactive precursor (prekallikrein) by the action of a Hageman factor fragment—prekallikrein activator; it acts primarily on high-molecular weight kininogen to form bradykinin (5). It is known that the plasma kallikrein-kinin system is activated in septic shock, and kinins could mediate the systemic vasodilation and increased capillary permeability seen in sepsis (4). We were unable to measure plasma prekallikrein or plasma kallikrein activity in this experimental model because of the very low activity of sheep kallikrein against the chromogenic substrate, S2302, which was used to measure plasma prekallikrein/kallikrein activity (19). However, we (3) previously measured plasma prekallikrein in nine patients with septic shock and acute renal failure. All patients had values below the normal range, suggesting activation of the plasma kallikrein-kinin system, and the survivors showed a return to normal during recovery (3). Therefore,

Table 1. Urine kallikrein excretion rate and plasma renin activity in control and aprotinin-treated groups (mean \pm SEM)

Control		Aprotinin	
Baseline	Sepsis	Baseline	Sepsis
<i>Urine kallikrein (nkat $\times 10^{-3}$ /min)</i>			
2.67 \pm 1.40	1.67 \pm 0.91	1.76 \pm 1.00	0.70 \pm 0.49
<i>Plasma renin activity (ng/mL/hr)</i>			
0.21 \pm 0.01	6.34 \pm 0.92 ^a	0.20 \pm 0.01	1.78 \pm 0.69 ^b
<i>(ng/L/sec)</i>			
0.06 \pm 0.003	1.76 \pm 0.25 ^a	0.06 \pm 0.003	0.49 \pm 0.19 ^b

^a $p < .05$ from baseline; ^b $p < .05$ from controls.

studies of the effect of protease inhibition in the experimental model of sepsis were of interest.

Aprotinin is a polypeptide protease inhibitor that is derived from bovine lung. It is active against a number of serine proteases, including trypsin, chymotrypsin, plasmin, and plasma and tissue kallikreins. Some studies (10) showed benefit from its use in acute pancreatitis, and aprotinin is now widely used to inhibit blood loss during cardiac surgery. Our results suggest that the hypotension and systemic vasodilation in early septic shock are prevented by aprotinin. This finding could be due to inhibition of any of the above protease enzymes, and our results do not allow discrimination between them. It is also possible that inhibition of neutrophil-derived proteases could be involved (20). Plasma kallikrein is known to be generated in septic shock and to be associated with appropriate biological effects. Experimental iv injection of kallikrein produces a picture that resembles septic shock, with hypotension and increased capillary permeability (21). It is possible that the beneficial effects seen in our studies reflect, at least in part, inhibition of endotoxin-induced kallikrein activity. Studies (22) using more selective inhibitors of the plasma kallikrein-kinin system, such as the recently synthesized kinin antagonists, are of interest in this respect. Recent findings using these agents in small animal models of endotoxemia tend to support a role of kinin generation in endotoxemic shock.

While aprotinin has been suggested to be useful in a wide range of disease states, to date it has not become routine therapy in any clinical situation. This finding probably is due, at least in part, to the use of inappropriately low dosages in previous studies (9, 10), such as the trials in acute pancreatitis. The dose regimes used in these studies were calculated on the basis of the affinity of aprotinin for glandular kallikrein ($K_i 9 \times 10^{-11}$), but the affinity of aprotinin for plasma kallikrein is considerably lower ($K_i 3 \times 10^{-8}$) (9). It is likely that in previous studies, adequate inhibition of the plasma

kallikrein-kinin system was not achieved (10). Recent work (23) demonstrated the feasibility and safety of using doses of aprotinin on the order of 20-fold higher than dosages used previously, which will achieve maximal plasma kallikrein inhibition (10). We used such a high dose in these studies, with apparent efficacy and no evidence of adverse effects.

As described above, the affinity of aprotinin for glandular (including renal) kallikrein is greater than for plasma kallikrein. In our studies, urine kallikrein excretion, which is thought to reflect activity of the renal kallikrein-kinin system, was lowest while the animals were receiving aprotinin. It is believed that the renal kallikrein-kinin system, which is anatomically and functionally distinct from the plasma system, promotes renal vasodilation and increased sodium excretion (20). Therefore, it is theoretically possible that aprotinin could adversely affect renal function during sepsis. However, we found evidence of improved renal function in the aprotinin group in our study. It has been suggested that the renal vasodilator function of the renal kallikrein-kinin system only becomes important in the face of reduced renal perfusion and/or activation of the renin-angiotensin system, in a manner analogous to the role of renal prostaglandins (21, 24). Kinins are a potent stimulus to the release of renal vasodilator prostaglandins (24). It seems likely that in our study, any potential adverse effect of renal kallikrein inhibition was outweighed by the improvement in systemic hemodynamics, and therefore, in renal perfusion and in the reduced plasma renin activity in the treatment group.

The increase in plasma renin activity in controls, which is a typical feature of experimental septic shock (14), was prevented by aprotinin treatment. This increase probably reflects the maintained systemic BP in the treatment group. However, it should be noted that kallikrein may be an important activator of prorenin. Kinins are known to stimulate renin release, and aprotinin has been shown to reduce plasma renin activity in normal man (25). It has been suggested (26) that renin and angiotensin II are important in the pathogenesis of acute renal failure, and angiotensin II potentiates sympathetic nervous system activity, which may also be important in the sepsis/acute renal failure syndrome. Prevention of renin-angiotensin stimulation may represent an additional beneficial outcome of aprotinin treatment in sepsis.

The apparent effect of aprotinin in preventing the increase in pulmonary artery pressure, maximal at 4 hrs postoperatively, is of some interest. It has been shown (8) that the increased pulmonary lymph flow, at 2 to 6 hrs after administration of endotoxin to sheep, is reduced by protease inhibition. It seems likely that

changes in pulmonary hemodynamics and permeability during sepsis reflect primarily cellular mechanisms, such as stimulation of neutrophils by complement activation (27). Our results suggest that pulmonary hypertension may reflect activation of protease enzymes against the active aprotinin. These enzymes could include neutrophil enzymes, although the affinity of aprotinin for neutrophil elastase and cathepsin G is relatively low (9). Tissue kallikrein recently was detected in the cytoplasm of human neutrophils (28). It is known that kinins have differing effects in various vascular beds, and cause pulmonary vasoconstriction in most species (4). This effect of aprotinin could have a beneficial effect on the course of septic shock, since it would be predicted to reduce lung water and improve right ventricular performance.

Further studies are in progress to establish the effect of aprotinin in established hypotensive septic shock. It seems clear that more selective and effective protease inhibitors will become available for assessment in the future, although it is possible that the relatively broad inhibitory spectrum of aprotinin may prove to be advantageous in the context of sepsis.

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Sampling site for blood lactate estimation: arterial or mixed venous?

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Abstract

It has been suggested that in patients with severe pulmonary pathology arterial lactate concentrations exceed mixed venous levels as a result of lactate production in the diseased lung.¹ This study was performed to examine the relationship between arterial and mixed venous (pulmonary arterial) whole blood lactate levels in critically ill patients. We studied 22 consecutive admissions to a general intensive care unit on one occasion each. All patients required systemic and pulmonary arterial catheterisation for the management of critical illness with lung involvement. Simultaneous arterial and mixed venous samples were drawn and analysed immediately on an automated analyser.

There was no significant difference between lactate levels in arterial (2.1 ± 0.3 mmol/l) and mixed venous (2.0 ± 0.32 mmol/l) blood. The bias between arterial and mixed venous values was 0.09 and the limits of agreement ($\pm 2SD$) were ± 0.38 mmol/l. The degree of correlation was excellent ($r = 0.99$).

There is no clinically important difference between mixed venous and arterial lactate. The arterial site for sampling blood to measure lactate remains relevant and practical.

Introduction

Blood lactate measurements have been used widely in the management and investigation of critical illness.²⁻⁴ Most clinicians and investigators have measured arterial lactate levels although there has been debate over the relative merits of plasma versus whole blood samples.⁵ It has been shown that patients suffering from lung cancer and pulmonary tuberculosis produce lactate in locally diseased areas of lung and that occasional patients have a significantly higher arterial lactate on the basis of this.¹ However, some investigators have used mixed venous samples preferentially to assess lactate levels in critically ill patients.⁶ Despite one previous study, the choice of sampling site for blood lactate measurement has not been satisfactorily resolved.⁷ We performed this study in an attempt to answer this question.

Key words:

Lactate

Arterial

Mixed venous

Methods

Twenty-two patients, mean age 60 years, range 39-80, were studied. All patients were mechanically ventilated, had arterial and pulmonary artery catheters *in situ* for standard clinical monitoring and were admitted consecutively into the study. Underlying diagnoses were: septic shock ($n = 16$), ARDS ($n = 18$), severe acute left ventricular failure ($n = 4$) and pneumonia ($n = 2$). Some patients fell into two diagnostic groups. Arterial and mixed venous samples were drawn simultaneously into heparinised syringes and immediately analysed using an automated analyser (Clandon Scientific, Farnborough, UK). Statistical analysis was by the graphical method of Bland and Altman⁸ and standard correlation coefficient. The technique of Bland and Altman requires the plotting of information derived from pairs of data points, the mean of the two values being plotted against their difference. The results are expressed as bias (mean difference) and limits of agreement (mean difference ± 2 SD). The study was approved by the local ethics committee.

Results

The arterial lactate levels were 2.1 ± 0.31 mmol/l and the mixed venous 2.0 ± 0.32 mmol expressed as mean \pm SEM.

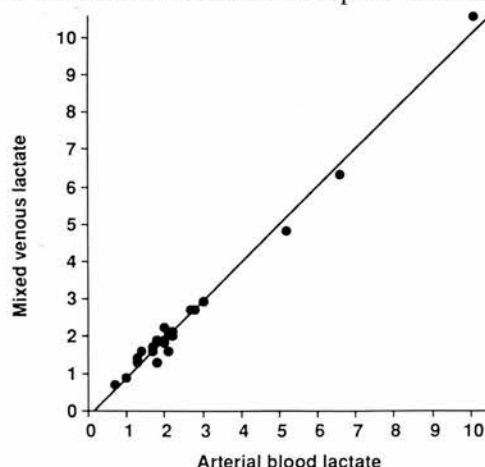


Figure 1 Relationship between arterial and mixed venous lactate concentrations ($r = 0.99$).

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If the catheter is introduced via the femoral artery the balloon can be detected as soon as it enters the inferior vena cava. If it is introduced via the superior vena cava, it cannot be seen until it has entered the right atrium. Once the tip of the pacing catheter has been located, an attempt can be made to place it against the wall. As the present results show, this was successful in almost all cases, as electrocardiography showed effective stimulation at a good or at least acceptable stimulation threshold. Minor corrections of the catheter position were nevertheless performed in some of these cases to achieve an even better stimulation threshold. Subsequent X-ray follow-up revealed that the tip of the catheter need not necessarily lie in the apex of the right ventricle for satisfactory stimulation results.

Problems in insertion occurred only when the balloon was overfilled with contrast medium and burst. Because Echovist® was developed for intravascular administration, serious toxic side-effects or micro-emboli are improbable in such an event. Furthermore, no such effects have been observed on intravascular administration of much larger amounts and higher concentrations.⁸

Ultrasound-guided positioning of a temporary pacing catheter was thus successful in almost 90% of cases. This readily available and safe procedure can be used as an alternative when a pacing catheter cannot be positioned under fluoroscopic control.

As an additional study in three patients confirmed, catheterisation of the pulmonary artery is also made easier with the above-described method. This applies in particular to intensive care patients in whom flow-directed positioning of such a catheter is unsuccessful and in whom radiographic monitoring is difficult, for example because of mechanical ventilation.

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degree of correlation was excellent ($r = 0.99$) as indicated in Figure 1. As shown in Figure 2 the bias was 0.09 with limits of agreement ± 0.38 (-0.47 to 0.29) which are well within the range of clinically significant changes in lactate concentration.

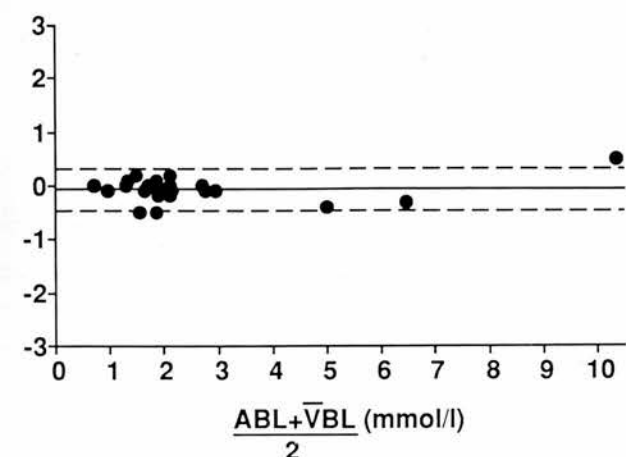


Figure 2 Bland-Altman plot of arteriovenous lactate difference versus mean concentration.

Discussion

Rochester and colleagues demonstrated the potential for diseased lung to produce lactate.¹ They concluded that this was a reflection of increased lung metabolism and speculated that the degree of arteriovenous difference in lactate might reflect the extent of diseased lung. We have been unable to demonstrate any difference between arterial and mixed venous lactate in a group of critically ill patients with much higher mean lactate levels than in the Rochester study and with quite different pathology. Even though there is no agreed threshold level for hyperlactaemia and that there is a persisting lack of consensus as to which sampling site is more appropriate, our findings would tend to confirm that there is no clinically significant difference between the two sites. Our findings are in keeping with those of Weil and colleagues who demonstrated apparently close agreement between arterial and central venous lactate concentrations in 12 patients studied prospectively and between mixed venous

(pulmonary arterial) lactate concentrations in 23 patients analysed retrospectively.⁷ In our study, however, only one paired sample was analysed from each consecutively enrolled patient, removing the possibility of bias. It would appear from these results that arterial lactate is at least as useful as mixed venous in these patients. It is also of interest to note that those investigators who have suggested levels of lactate which might be deemed significant have used arterial measurements.²⁻⁴

Since serial measurements are of greater utility in the monitoring of shock than single measurements^{9,10} it seems prudent to choose one site and repeat measurements from it. However, arterial sampling for blood lactate determination remains clinically relevant and practical.

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Evaluation of alpha-1-antichymotrypsin as an indicator for infections in multi-traumatised patients

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Summary

Serum concentrations of alpha-1-antichymotrypsin (ACT) and C-reactive protein (CRP) were determined to evaluate the predictive value of these acute phase reactants with regard to infective complications in polytraumatised patients. Because trauma itself stimulates the synthesis of both proteins, a series of patients with well-defined injuries was used as additional controls. Therefore, in addition to polytraumatised patients with and without infections, both variables were measured in the serum of patients having had extensive orthopaedic surgery. Serum concentrations of both proteins increased within 24-48 hrs after accidental or iatrogenic tissue damage. In correlation with the severity of their injuries, multi-traumatised patients reached higher serum concentrations than patients with hip joint operations. However, in polytraumatised patients suffering from infections, concentrations of ACT increased to maximum values of 1.3-1.6 g/l. Often the increase of ACT began before the episode of infection became clinically evident. However, whereas CRP values often varied widely from day to day in the same individual, ACT values above 1.2 g/l reliably indicated an infectious complication in polytraumatised patients. The results suggest that ACT could be used as an aid to the diagnosis of infective complications in multi-traumatised patients.

Introduction

Various inflammatory stimuli result in the initiation of the so-called 'acute phase response'.^{1,2} In addition to infections, other stimuli include physical trauma, burns, intoxications or neoplasms.³⁻⁵ One of the basic features of the acute phase reaction is the increase in certain serum proteins⁶⁻⁸ collectively denominated as acute phase proteins (APP). Most of these proteins are synthesised by hepatocytes, stimulated by various cytokines ie interleukin-1, interleukin-6 or tumour necrosis factor.^{9,10} Serum levels of some APPs are furthermore influenced by steroid therapy, oestrogens, impaired renal function and phenotypic variants.^{6,11} One of

Key words:

Alpha-1-antichymotrypsin

Infections

Multi-traumatised patients

the most widely studied APPs is C-reactive protein (CRP).

Hitherto, little attention has been paid to another APP, alpha-1-antichymotrypsin (ACT), a serum glycoprotein with a molecular weight of about 59 kDa.¹⁶ In healthy individuals its serum concentration ranges from 0.2 to 0.6 g/l. Its synthesis by hepatocytes is stimulated by several cytokines.^{17,18} The main function of ACT is to inhibit chymotrypsin-like proteases.¹⁹ Furthermore, ACT is able to modulate the immune response by inhibition of the natural cytotoxic activity of killer lymphocytes²⁰ and enhancement of the antibody response.²¹

In burned patients, and post-abdominal and heart surgery, serum concentrations of ACT markedly increased within 24-48 hrs of the tissue injury.^{4,5,22} However, as yet, little information exists about non-infectious and infectious influences in multi-traumatised patients, in which high levels of ACT may be induced by severe tissue injuries. Therefore, CRP and ACT were measured in the sera of multi-traumatised patients with and without infections in order to define those concentrations that differentiate between tissue injuries and infectious complications. To quantify the reaction strictly due to tissue injury, a group of orthopaedic patients was included in this study for comparison.

Methods

Patients

The study comprised 42 multi-traumatised patients admitted to the surgical intensive care unit of the University of Giessen requiring mechanical ventilation for at least 48 hrs. Patients suffering from hepatic injury or hepatic failure during their stay on the intensive care unit were excluded from the study. To study the influence of tissue injuries on ACT serum concentrations a group of orthopaedic patients with uncomplicated recovery after joint operations (endoprosthetic hip joint replacement, duration of operation 75-325 minutes) was included as controls. Patient characteristics and clinical data are given in Table 1.

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Original Article

Acid–base responses to high-volume haemofiltration in the critically ill

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Abstract. We have studied the acid–base and cardiorespiratory effects of intermittent pumped high-volume venovenous haemofiltration (HVHF) using replacement fluid containing lactate as the source of bicarbonate in critically ill patients. We demonstrated significant hyperlactataemia throughout the procedure, but there was no deterioration in acid–base status, haemodynamics, or oxygen delivery. These observations suggest that the worsening of acidosis and the hypotension that have been described with this technique [1] can be avoided by appropriate monitoring and resuscitation prior to haemofiltration, and may be due to unrecognized inadequacies in the oxygen transport system.

Key words: haemofiltration; acute renal failure; acid–base disturbance

Introduction

The last decade has witnessed major changes in the use of renal replacement therapy (RRT), particularly in unstable and severely ill patients [2]. This has been in great part due to the improved haemodynamic stability which we and others have demonstrated with haemofiltration as opposed to haemodialysis [3,4]. Since the introduction of continuous spontaneous haemofiltration by Kramer there has been a rapid adoption of haemofiltration techniques in intensive-care units and acute nephrology wards [5]. Refinements and advances in the form of continuous (spontaneous or pumped) haemofiltration and intermittent machine-pumped HVHF have logically followed [6,7]. The choice of treatment modality will be influenced by factors such as the patient's clinical state and underlying diagnosis, and local differences such as the type of unit and the availability of staff trained in the use of different types of RRT. We use HVHF with lactate-containing replacement fluid for our patients with acute renal failure (ARF) as part of multiple-organ failure. It has been suggested that these patients with

cardiovascular instability may not tolerate lactate administration because of failure to metabolize lactate [1], and may suffer haemodynamic deterioration as a result.

We investigated the acid–base and cardiorespiratory effects of treatment with HVHF and lactate-containing replacement fluid in 12 critically ill patients with multiple-organ failure.

Subjects and methods

Twelve patients with established multiple-organ failure undergoing intermittent pump-driven HVHF were each studied on one occasion. Clinical details of the patients, including admission Apache II scores, are given in Table 1. Haemofiltration was undertaken as treatment for acute renal failure (ARF) in 11 patients and in an attempt to improve gas exchange in one patient with severe adult respiratory distress syndrome (ARDS). All patients were mechanically ventilated and had femoral arterial lines and thermodilution pulmonary artery flotation catheters for standard clinical monitoring. Cardiorespiratory status was optimized before haemofiltration in all patients. Fluids and vasoactive drugs were titrated to achieve previously described therapeutic goals [8], (cardiac index: $CI > 4.5$ l/min/m²; oxygen delivery: $DO_2 > 600$ ml/min/m²; mean arterial blood pressure: $MAP > 70$ mmHg). Eleven patients required vasoactive drugs, and in nine of these a combination of catecholamines (adrenaline or dobutamine with noradrenaline) was necessary to reverse hypotension and maintain high cardiac output. The study period was from just before haemofiltration until 1 h after its finish. During this period there were no changes to sedation or ventilator settings, or increases in catecholamine infusion rates, although three patients required reductions in these because of increasing blood pressure during HVHF. Extra fluid administration by bolus was not required in any patient.

Haemofiltration was performed using a Gambro AK 10 system with a FH 77 hollow-fibre filter, and vascular access was through a double-lumen catheter in an internal jugular or subclavian vein. A blood flow rate of 200–300 ml/min and transmembrane pressure of 300–400 mmHg were used to achieve an initial filtration rate of 100–120 ml/min although the filtration rate tended to decline as the treatment progressed.

Anticoagulation was with heparin administered into the afferent limb of the circuit to achieve an activated clotting time (ACT) 30 s above baseline, or over 180 s. The replace-

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Table 1. Clinical data

	Sex	Age	Diagnosis	APACHE II	Outcome
1	F	63	Shock, rhabdomyolysis	43	S
2	F	53	ARDS, septic shock	21	S
3	M	80	Septic shock, ARDS	29	NS
4	M	63	Septic shock, ARDS	21	NS
5	F	54	Septic shock, ARDS	18	S
6	M	77	Septic shock, ARDS	41	NS
7	F	58	Septic shock	27	S
8	M	72	Acute pancreatitis, septic shock	20	NS
9	F	68	Candida, septic shock, ARDS	29	NS
10	F	65	Septic shock, ARDS	25	NS
11	M	73	Septic shock, ARDS	33	NS
12	M	68	Septic shock, liver failure	21	NS

ment fluid was Haemofiltrasol 22 (Gambro) containing lactate 45 mmol/l, Na^+ 140 mmol/l, Ca^{2+} 1.6 mmol/l, Mg^{2+} 0.75 mmol/l, Cl^- 100 mmol/l with potassium added as required. The mean duration of treatment was 3 h 50 min (range 2 h 30 min to 6 h 15 min) and mean lactate infusion was 696 mmol (range 450–1080 mmol).

Prior to haemofiltration a full cardiorespiratory profile was obtained. Heart rate, mean arterial pressure (MAP), central venous pressure (CVP), and end-expiratory pulmonary artery balloon occluded pressure (PAOP) were recorded. Cardiac output was measured by thermodilution using an average of three injections of 10 ml cooled ($<10^\circ\text{C}$) 5% dextrose. Cardiac index (CI) and systemic vascular resistance index (SVRI) were calculated from standard formulae. In all patients simultaneous samples of arterial and mixed venous (pulmonary arterial) blood were obtained within 1 min of the last cardiac output measurement. Oxygen tension (pO_2), oxyhaemoglobin saturation (sO_2), carbon dioxide tension (pCO_2), hydrogen ion concentration ($[\text{H}^+]$), and haemoglobin concentration were measured by a Corning 278 blood gas analyser and a Corning 2500 co-oximeter. Arterial and mixed venous oxygen contents were calculated using standard formulae, and in conjunction with CI measurements, oxygen delivery (DO_2) and oxygen consumption (VO_2) were derived. At the time of blood sampling 1.5 ml of arterial blood was placed into preweighed glass tubes containing 5 ml 5% perchloric acid, immediately refrigerated and subsequently analysed for whole blood lactate concentration by an enzymatic method monitoring the rate of formation of NADH from NAD in the presence of lactate dehydrogenase. The assay was carried out in 0.5 M glycine buffer (pH 9.6) containing 0.2 M hydrazine hydrate and 5.4 mM EDTA. The reaction was monitored fluorimetrically on a Cobas Bio (Roche) centrifugal analyser and whole blood lactate calculated assuming a whole blood density of 1.06. Interassay coefficient of variation was $<10\%$ over the working range. All measurements were repeated hourly during HVHF and at 1 h after treatment.

Statistical analysis was by a Wilcoxon signed rank sum test comparing pretreatment values with those at each hour during and following HVHF. All results are expressed as mean \pm SEM.

Results

The results for the ARDS patient were similar to the 11 ARF patients so the results are presented together,

and summarized in Tables 2 and 3. Haemofiltration was well tolerated in all patients. There were minor falls in MAP, CI and DO_2 but these were not statistically significant. SVRI and VO_2 showed increases during the treatment, but these changes were not significant.

Lactate levels rose quickly (pre: 1.7 ± 0.3 mmol/l; 1 h: 5.6 ± 0.4 mmol/l; $P < 0.0001$) and were still elevated, although not significantly (2.6 ± 0.4 mmol/l; $P = 0.06$), 1 h after HVHF. Baseline arterial and mixed venous $[\text{H}^+]$, $[\text{HCO}_3^-]$ and pCO_2 were not significantly different. Arterial and mixed venous $[\text{H}^+]$ tended to decrease, and $[\text{HCO}_3^-]$ tended to increase although none of these achieved statistical significance. There were no significant changes in blood gas measurements. Four of the 12 patients survived.

Discussion

In this and a previous study [4] we have demonstrated that HVHF is well tolerated in a potentially unstable group of patients with multiple-organ failure. In our previous group of patients there were significant declines in CVP and CI with blood pressure maintained by vasoconstriction. In the present study we have not confirmed these findings, and this probably reflects the clinical and haemodynamic heterogeneity of small groups of critically ill patients. What we have confirmed is the haemodynamic stability of HVHF in these patients.

The mechanisms for the handling of increased blood lactate in critically ill patients with multiple-organ failure are widely discussed, but are commonly misunderstood [9–11]. The arterial blood lactate level (ABL) is a reflection of the balance of lactate entering the circulation (exogenous or endogenous) and lactate removal, mainly by the liver. In shock, sepsis, and ARDS splanchnic blood flow is abnormal and the ability of the tissues to utilize oxygen is impaired [12,13]. In view of this there are theoretical concerns over the ability of the liver to handle the large, acute lactate load which is administered during HVHF. Davenport and colleagues have shown that in their patients with ARF, with or without liver failure, there

Table 2. Effects of HVHF on cardiorespiratory status

	Pre	1 hour	3 hours	1 hour post	
HR (b.p.m.)	106.4 ± 3.9	103.2 ± 3.9	107 ± 5	106 ± 4.7	NS
CI (l/min/m ²)	4.8 ± 0.2	4.1 ± 0.3 (<i>P</i> = 0.07)	4.2 ± 0.3	4.7 ± 0.3	NS
CVP (mmHg)	15.8 ± 1.2	13.3 ± 1.2	14.5 ± 1.2	14.8 ± 1.6	NS
MAP (mmHg)	75.8 ± 3.9	72 ± 4.1	73.6 ± 4.5	76.3 ± 3.9	NS
PAOP (mmHg)	14.3 ± 0.9	13.5 ± 0.9	13.7 ± 0.9	14.8 ± 1	NS
SVRI (dynes/cm ⁵ m ²)	1034 ± 69	1183 ± 107	1197 ± 105	1097 ± 82	NS
DO ₂ (ml/min/m ²)	718 ± 44	641 ± 45	647 ± 47	684 ± 48	NS
VO ₂ (ml/min/m ²)	150 ± 7.25	149 ± 7	160 ± 8	154 ± 6	NS

Table 3. Effects of HVHF on lactate, blood gas and acid base status

		Pre	1 hour	3 hour	1 hour post	
Arterial	Lactate (mmol/l)	1.7 ± 0.3	5.6 ± 0.4***	6.9 ± 0.3***	2.6 ± 0.4	NS
	H ⁺ (mmol/l)	50 ± 3	51 ± 3	48 ± 2.7	43 ± 2	NS
	PCO ₂ (kPa)	6.2 ± 0.5	5.7 ± 0.4	5.6 ± 0.4	6.1 ± 0.4	NS
	PO ₂ (kPa)	13 ± 1	13 ± 1	15 ± 1.5	13 ± 1.5	NS
	HCO ₃ (mmol/l)	23.7 ± 2	20.9 ± 1	21.9 ± 1	25.8 ± 1	NS
	SO ₂ (%)	94 ± 1	94 ± 1	95 ± 1	94 ± 1	NS
Mixed venous	H ⁺ (mmol/l)	51 ± 3	53 ± 3	49 ± 3	45 ± 2	NS
	PCO ₂ (kPa)	6.9 ± 0.5	6.2 ± 0.5	6.3 ± 0.6	6.7 ± 0.6	NS
	PO ₂ (kPa)	5.4 ± 0.3	5.3 ± 0.3	5.2 ± 0.3	5.2 ± 0.2	NS
	HCO ₃ (mmol/l)	23.3 ± 2	20.7 ± 1	22.2 ± 1.3	25.8 ± 1	NS
	SO ₂ (%)	74 ± 2	72 ± 2	72 ± 2	73 ± 2	NS

*** *P* < 0.001

were significant declines in MAP and serum (arterial) bicarbonate [1]. In the hepatorenal group there was a significant increase in [H⁺].

In contrast, our studies have not shown any significant hypotension, although in both of our studies the initial MAP was lower than their ARF group, and equivalent to the hepatorenal group. In our current study we have shown that there is no deterioration in arterial or mixed venous acid–base status during HVHF, despite higher peak lactate levels: 6.9 ± 0.3 mmol/l at 3 h. We chose to measure mixed venous gases and acid–base status on account of the studies of Adroque *et al.* [15] and Weil's group [16], which have suggested that the central or mixed venous sampling site is more sensitive to the acid–base changes in the microcirculation than is systemic arterial sampling. We have shown that this is not the case for blood lactate levels [17]. In the current study we showed no significant difference between arterial and mixed venous acid–base parameters throughout the study period, and there were no adverse effects on [H⁺] or [HCO₃] in our patients.

It has been suggested that the adverse acid–base responses and hypotension seen in previous studies may be due to reduced tissue oxygen delivery [1]. This seems likely, as it has been shown repeatedly that clinical assessment of the cardiorespiratory system in critically ill patients is inaccurate [18,19]. It is widely accepted that MAP may be reasonably maintained despite low cardiac filling pressures, CI and DO₂. In our patients these variables were measured prior to

haemofiltration, and appropriate resuscitation was carried out in an attempt to increase CI and DO₂ whilst maintaining MAP near normal.

In contrast to our study population, that of Davenport and co-workers contained six patients with overt hepatic failure. These patients are notoriously resistant to resuscitation, even with high doses of vasopressors. It would, however, be of interest to study this group of patients in the manner which we have described, perhaps adding acetylcysteine infusion in those with hepatic failure secondary to self-poisoning with paracetamol [20].

The results of this study suggest that HVHF with lactate-containing fluid may be a satisfactory form of RRT in critically ill patients. In our patients it was accomplished without deterioration in acid–base status or cardiorespiratory function, despite theoretical objections concerning the exogenous lactate load. This may be a reflection of prior resuscitation, aiming to maintain high DO₂ and normal MAP, but further study is required to confirm this.

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Haemodynamic and oxygen transport effects of propofol infusion in critically ill adults

G. R. NIMMO, S. J. MACKENZIE AND I. S. GRANT

Summary

The effects of a sedative infusion of propofol on haemodynamics and oxygen transport were examined in critically ill adult patients. Ten patients receiving mechanical ventilation for treatment of septic shock and respiratory failure were given a decreasing rate propofol infusion designed to achieve and maintain a stable sedation level. Full cardiovascular and oxygen transport variables, arterial blood lactate concentrations and sedation scores were measured before infusion and at 1, 3 and 6 h after starting the infusion. There were significant reductions in mean (SEM) heart rate (97.3(2.9) to 85.7(3.9) $\text{beat}\cdot\text{min}^{-1}$ $p < 0.05$), mean arterial pressure (87.6(3.7) to 76.2(4.1) mmHg $p < 0.05$) and systemic vascular resistance index (1461(137) to 1327(141) $\text{dyne}\cdot\text{s}\cdot\text{cm}^{-5}\cdot\text{m}^{-2}$ $p < 0.05$), with no significant change in cardiac filling pressures. There were no significant changes in cardiac output, oxygen delivery, oxygen consumption or arterial blood lactate concentrations. Controlled propofol sedation is well tolerated in appropriately monitored and resuscitated critically ill adult patients, and appears to have no major effects on whole-body oxygen transport.

Key words

Anaesthetics, intravenous; propofol.
Oxygen; transport.

Maintenance of tissue oxygen delivery at a rate sufficient to meet demand is pivotal to a successful outcome in critical illness. In many clinical situations, such as septic shock (SS) and adult respiratory distress syndrome (ARDS), there is a defect of tissue oxygen utilisation so that oxygen consumption ($\dot{V}\text{O}_2$) is dependent on oxygen delivery, even when the latter is normal or supranormal [1,2]. In low cardiac output states, such as cardiogenic shock, oxygen extraction is generally maintained or increased with resultant reduction in mixed venous oxyhaemoglobin saturation (SvO_2). In either situation the balance of oxygen delivery to consumption is critical, and may be crucially affected by changes in either oxygen delivery or tissue oxygen demand. Factors which can affect demand include sedation, muscle relaxation and mechanical ventilation.

Propofol is being increasingly used as a sedative agent in the intensive care unit. Like other sedatives it has the potential to affect the oxygen supply/demand relationship both detrimentally by decreasing cardiac output and thus oxygen delivery, and beneficially by reducing oxygen demand. When used for induction and maintenance of anaesthesia, it has been shown to have a number of haemodynamic effects including substantial reductions in heart rate, cardiac output, arterial blood pressure and systemic

vascular resistance [3]. However, the precise cardiorespiratory effects of subanaesthetic doses used for sedation in critically ill patients dependent on vasoactive drugs for haemodynamic stability have not been investigated rigorously. The aim of this study was to document the effects of a sedative infusion regimen of propofol on haemodynamics, oxygen transport and blood lactate. Furthermore, in an attempt to unravel the mechanism of any effect on $\dot{V}\text{O}_2$, resuscitation with fluid and/or vasoactive drugs would be used after 3 h sedation to restore mean arterial blood pressure (MAP), cardiac output and oxygen delivery to baseline values. Subsequently, any residual decrease in $\dot{V}\text{O}_2$ could then be attributed to a decrease in oxygen demand. Blood lactate concentrations were measured as a further index of the adequacy of tissue oxygenation.

Methods

Ten severely ill adult patients receiving mechanical ventilation and with femoral and pulmonary artery catheters *in situ* for standard monitoring were studied with the informed consent of their next of kin and the approval of the local ethics committee. All had been resuscitated initially using combinations of colloid fluid and blood to

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achieve optimal pulmonary artery occlusion pressure (PAOP) with the addition of an inotrope and/or vasopressor to achieve a stable cardiac index (CI) $> 4 \text{ l.min}^{-1}.\text{m}^{-2}$ with MAP $> 80 \text{ mmHg}$. They had all become haemodynamically stable, and were receiving unchanged doses of vasoactive agents for at least 2 h before the start of the study.

All patients received papaveretum at a fixed infusion rate for 6 h before and throughout the study, other sedation having been discontinued several hours earlier; the study began when the patients required further sedation. No muscle relaxants were used. Immediately before commencing the propofol infusion baseline measurements were made of heart rate (HR), mean arterial pressure, mean central venous pressure (CVP), mean pulmonary artery pressure (PAM), end-expiratory pulmonary artery occlusion pressure and cardiac output measured in triplicate using 10 ml of 5% dextrose with a measured in-line temperature $< 10^\circ\text{C}$ (Series 7000 monitor, Marquette, Milwaukee). Patients' height and weight were measured and the following derived variables were calculated using standard formulae; cardiac index (CI), stroke volume (SV), stroke volume index (SVI), ventricular stroke work index (right: RVSWI; left: LVSWI), systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI).

Femoral and mixed venous (pulmonary arterial) blood were sampled for measurement of blood gas tensions, hydrogen ion concentration, haemoglobin concentration and oxyhaemoglobin saturations. Oxygen delivery and consumption were calculated, the latter using the inverse Fick relationship. Simultaneously, assessment was made of conscious level using the Ramsay sedation score [4] and arterial whole blood lactate concentration was measured using an automated analyser (Clandon Scientific, Farnborough, UK).

Propofol was infused according to a decreasing infusion rate regimen designed on the basis of known pharmacokinetic data to rapidly achieve and maintain a blood concentration of $1 \mu\text{g.ml}^{-1}$ [5]. The infusion ran at $4 \text{ mg.kg}^{-1}.\text{h}^{-1}$ for 10 min, $3 \text{ mg.kg}^{-1}.\text{h}^{-1}$ for 50 min and then $2 \text{ mg.kg}^{-1}.\text{h}^{-1}$ for the remaining 5 h of the study. Cardiovascular measurements were repeated 10 and 30 min after commencement of propofol infusion, and then all measurements (haemodynamic, oxygen transport, lactate and sedation score) were repeated at 1 h, 3 h and 6 h. In six patients modified pulmonary artery catheters (PACs) with fast thermistors were inserted and right ventricular ejection fraction (RVEF) and volumes were measured (REF-1, Baxter-Edwards, California, USA). No patient had to be withdrawn from the study because of clinically important decreases in MAP or cardiac output. After 3 h of propofol sedation, cardiac output and oxygen delivery were restored to as near baseline as possible using a combination of fluid (plasma protein solution) to restore PAOP, and/or vasoactive drugs as appropriate.

Statistical analysis was carried out using the Wilcoxon signed rank test to compare paired data at baseline and 3 h. All values are expressed as mean (SEM). Variables at 6 h were not analysed since manipulation had resulted in a restoration to initial values.

Results

The clinical details of the 10 patients studied are shown in Table 1, and the cardiorespiratory data at the individual study points are detailed in Table 2. Heart rate, MAP, cardiac index and SVRI are shown in Figure 1, and oxygen delivery, $\dot{V}\text{O}_2$ and Ramsay sedation score in Figure 2. Infusion of propofol was associated with significant reductions in HR, mean arterial pressure and systemic vascular resistance index. Stroke volume and, in the six patients

Table 1. Details of patients.

Patient No.	Age (years)	Weight (kg)	APACHE Score	Diagnosis	Inotrope	Therapy at 3h
1	67	80	22	Acute pancreatitis ARDS	Dobutamine	Dobutamine
2	78	60	24	Septic shock Oesophago-gastrectomy Septic shock ARDS	Dobutamine	Dobutamine Plasma protein solution
3	48	80	21	G-I haemorrhage Septic shock	Noradrenaline	Noradrenaline
4	70	75	21	Acute pancreatitis Septic shock	Dobutamine	Dobutamine
5	70	80	23	Septic shock Post-cystectomy	Adrenaline Noradrenaline	Plasma protein solution
6	81	80	29	Pneumonia Mitral valve disease	Adrenaline Dopamine	Dobutamine
7	64	70	15	Perforated duodenal ulcer Septic shock Acute renal failure	Dopamine	Dopamine Plasma protein solution
8	67	45	31	Septic shock Acute renal failure	Dopamine	Dopamine
9	74	75	22	Perforated colon Septic shock ARDS	Dobutamine Dopamine Noradrenaline	No change
10	76	85	23	Perforated duodenal ulcer Septic shock ARDS	Dobutamine Noradrenaline	No change

ARDS, adult respiratory distress syndrome; G-I, gastro-intestinal.

Table 2. Mean (SEM) cardiovascular and oxygen transport variables, whole blood lactate, and sedation scores before and during propofol infusion.

	Before	30 min	60 min	3 h	6 h
HR; beat.min ⁻¹	97.3 (4.0)	93.6 (2.9)	91.5 (3.6)	85.7 (3.9)*	96.0 (5.3)
MAP; mmHg	87.6 (3.7)	78.4 (3.4)	79.8 (3.7)	76.2 (4.1)*	85.2 (2.7)
CVP; mmHg	12.4 (1.5)	11.1 (1.2)	11.3 (1.2)	11.3 (1.0)	12.4 (1.2)
PAWP; mmHg	14.2 (1.5)	11.5 (1.6)	12.1 (1.4)	12.7 (1.5)	13.4 (1.5)
CI; l.min ⁻¹ .m ⁻²	4.44 (0.42)	4.43 (0.45)	4.3 (0.39)	4.13 (0.36)	4.36 (0.40)
SVI; ml.min ⁻²	46.2 (4.8)	48.3 (5.6)	48.2 (4.6)	49.2 (4.5)	47.2 (5.7)
LVSWI; g.m.m ⁻²	46.1 (5.8)	43.0 (4.0)	42.4 (3.9)	41.1 (3.0)	46.0 (5.8)
RVSWI; g.m.m ⁻²	13.3 (2.0)	11.7 (1.9)	11.6 (1.6)	11.6 (1.5)	11.5 (2.0)
RVEF%; (n = 6)	38.7 (4.8)	39.5 (5.9)	42.0 (6.1)	37.5 (4.9)	33.7 (5.3)
SVRI; dynes.s.cm ⁻⁵ .m ⁻²	1461 (137)	1360 (166)	1405 (180)	1327 (141)*	1435 (132)
Oxygen delivery; ml.min ⁻¹ .m ⁻²	660 (66)		632 (58)	596 (54)	641 (70)
$\dot{V}O_2$; ml.min ⁻¹ .m ⁻²	132 (9)		130 (8)	122 (5)	130 (6)
Lactate; mmol.l ⁻¹	0.98 (0.11)		1.09 (0.14)	1.07 (0.12)	1.07 (0.11)
Sedation score	2.65 (0.27)	4.65 (0.42)	4.8 (0.50)	5.0 (0.29)**	4.7 (0.42)

HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; PAWP, pulmonary artery wedge pressure; CI, cardiac index; SVI, stroke volume index; LVSWI, left ventricular stroke work index; RVSWI, right ventricular stroke work index; RVEF, right ventricular ejection fraction; SVRI, systemic vascular resistance index; $\dot{V}O_2$, oxygen consumption.

*p < 0.05 3 h vs baseline values.

**p < 0.01 3 h vs baseline values.

where it was measured, the RVEF was unchanged. There were no significant changes in CVP or PAOP across the group, but in three patients (nos. 2, 7 and 10) there were marked decreases requiring fluid infusion to restore filling pressures and cardiac output at 3 h but not before. In parallel with cardiac output, there was a trend towards a reduction in oxygen delivery at 3 h, but this did not achieve statistical significance. There was a similar trend in $\dot{V}O_2$. No significant change was noted in blood lactate concentrations. As anticipated, the mean (SEM) Ramsay sedation

score at 3 h changed significantly from 2.65(0.27) to 5.0(0.29).

The therapeutic interventions required to restore cardiac output and oxygen delivery are shown in Table 1, and their effects on haemodynamics and oxygen transport in Table 2 and Figures 1 and 2. HR, MAP and $\dot{V}O_2$ were successfully restored to baseline, oxygen delivery and $\dot{V}O_2$ rising in parallel, and there were no changes in lactate concentrations or sedation level.

Discussion

We have demonstrated that propofol infusion, given in an infusion regimen designed to achieve rapidly and maintain a blood level of 1 $\mu\text{g.ml}^{-1}$, is not associated with clinically significant haemodynamic or oxygen transport effects in adequately resuscitated adult critically ill patients.

The haemodynamic effects of propofol anaesthesia have been extensively investigated and are well documented [3]. Propofol induction of anaesthesia produces a dose-related reduction in blood pressure which has been attributed both to reduced cardiac output and to a reduction in SVRI [6,7].

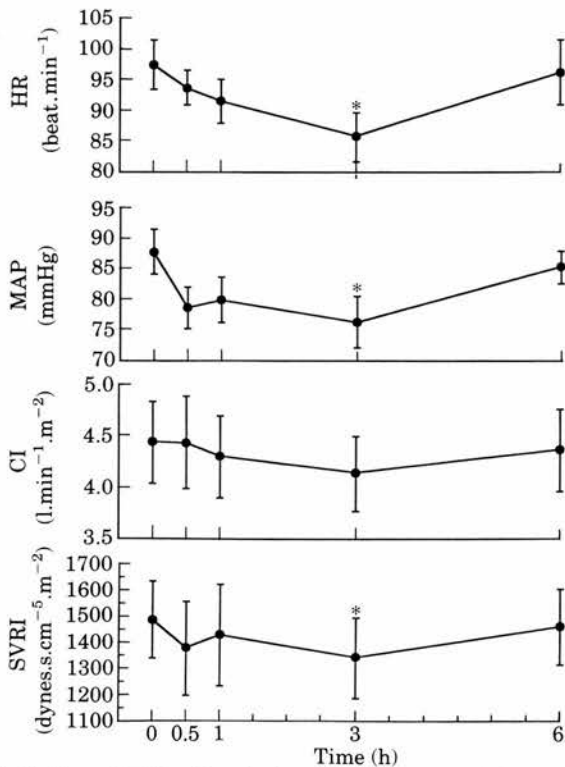


Fig. 1. Mean (SEM) values for heart rate, mean arterial pressure, cardiac index and SVRI during propofol infusion in 10 severely ill adult patients on mechanical ventilation. HR, heart rate; MAP, mean arterial blood pressure; CI, cardiac index; SVRI, systemic vascular resistance index. *p < 0.05.

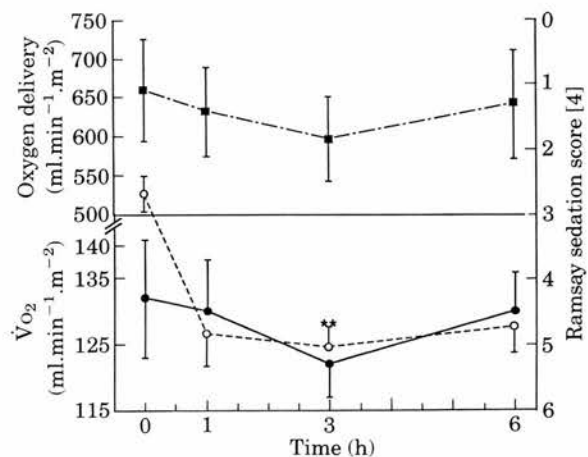


Fig. 2. Mean (SEM) values for oxygen delivery (---■---), oxygen consumption (---●---), and Ramsay sedation score (---○---) during propofol infusion in 10 severely ill patients. **p < 0.01.

The mechanism of the reduction in cardiac output is a direct depression of myocardial contractility [7], which according to some workers may be coupled with decreased preload [8]. Nevertheless, many investigators have found no effect on preload, attributing the fall in cardiac output to a direct negative inotropic effect alone [6,7].

During infusion maintenance of anaesthesia SVRI tends to increase back towards baseline or above, especially with surgical stimulation, and cardiac output remains below baseline [6,9]. Heart rate tends to decline during propofol maintenance, due both to increased vagal tone and to the resetting of baroreceptor reflex activity [10].

Propofol has recently been introduced as a sedative agent for use in Intensive Care. Initial studies have reported a hypotensive effect, sufficient in one study to prompt infusion rate reductions in some patients [11]. Other investigators have found little difference in cardiovascular effects when comparing propofol with midazolam [12]. Given the accepted importance of the maintenance of supranormal cardiac output and oxygen delivery, whilst concurrently assuring an adequate MAP in the treatment of patients with many types of critical illness [13], it is surprising that until now there has been little detailed data on the cardio-respiratory effects of propofol in such patients.

We have shown that propofol is well tolerated in a group of extremely sick patients who are dependent on vasoactive drugs. The study protocol avoided the use of bolus doses since it is our experience that even doses as low as 0.5 mg.kg^{-1} given intravenously over 1 min may lead to significant hypotension. The infusion protocol was based on pharmacokinetic data from critically ill patients, and was geared to achieve and maintain a blood concentration of around $1 \mu\text{g.ml}^{-1}$ [5]. In fact all patients were excessively sedated at this concentration, probably reflecting their severity of illness (APACHE II mean 23; range 15–31) since it has been shown that the higher a patient's APACHE II score the less will be the sedation requirement [14]. At the end of the study period, propofol infusion rates were reduced to clinically appropriate rates.

In no patient did the infusion rate require reduction from the protocol as a result of severe adverse haemodynamic effects. The decrease in blood pressure was acceptable, remaining close to the value aimed for with resuscitation, while cardiac output did not decrease to a statistically significant degree. Interestingly, stroke volume and RVEF were maintained, any reduction in cardiac output being attributable to the reduction in HR. It may be that after-load reduction led to maintenance of stroke volume despite myocardial depression. Although pooled group data on filling pressures did not show any overall change, three patients suffered substantial reductions of PAOP which, without volume expansion, would have led to reduced cardiac output. Overall, our results show that propofol in sedative dosage is free from significant myocardial depressant effects, but that hypotension occurs due to the combination of a reduction in heart rate (and hence cardiac output) and a slight reduction in SVRI, possibly as a consequence of reduced sympathetic activity. The finding of three patients with falls in PAOP suggests that in less well fluid resuscitated patients, venodilatation and reduced filling pressure is a potential problem. Reattainment of the baseline values of cardiac output proved straightforward, requiring fluid in three patients and small increases in inotrope infusion rate in seven patients.

The importance of achieving and maintaining a high oxygen delivery when treating critically ill patients has been emphasised by a number of workers, on account of the phenomenon of pathological delivery-dependent oxygen consumption, which has been documented both in septic shock and ARDS [1,2], and the increased survival associated with attainment of optimal oxygen delivery in septic shock [15]. Delivery dependence is due to an inability of some tissues to regulate oxygen extraction normally, and may imply a persistent tissue oxygen debt, with oxygen demand in excess of actual consumption. We have recently shown that this abnormality may be present despite normal blood lactate concentrations [16].

In the normal human where oxygen consumption meets demand, sedation, anaesthesia, muscle relaxation and assisted ventilation should all reduce $\dot{V}\text{O}_2$ because of the fall in requirements. Similarly, in patients with low flow conditions, such as cardiogenic shock, where critical reductions in oxygen delivery are present and $\dot{V}\text{O}_2$ is maintained by avid oxygen extraction, mechanical ventilation will reduce the oxygen cost of breathing, and thus tissue oxygen requirements, and will improve the oxygen supply/demand balance [17]. It is less clear, however, how sedation affects the balance of oxygen supply, utilisation and demand in critical illnesses such as septic shock and ARDS. The fact that sedation is generally associated with decreased myocardial oxygen demand, and with reduced cerebral metabolic rate for oxygen, suggests that there should be a beneficial effect on whole body $\dot{V}\text{O}_2$. Conversely, if the sedation also results in falls in cardiac output and oxygen delivery in the presence of pathological delivery-dependent oxygen consumption, $\dot{V}\text{O}_2$ may decrease to a greater extent than demand, with aggravation of the oxygen shortfall.

This study does not reveal a significant reduction in oxygen delivery associated with propofol sedation. However, there is a trend towards a parallel reduction in both oxygen delivery and $\dot{V}\text{O}_2$. Therapeutic interventions which restored oxygen delivery also tended to increase $\dot{V}\text{O}_2$, although sedation level was unchanged. No significant changes in blood lactate concentrations, which might have helped clarify the effects on tissue oxygenation, occurred. In critically ill patients with pathological delivery-dependent $\dot{V}\text{O}_2$, sedation may lead to reductions in $\dot{V}\text{O}_2$ which are linked to changes in oxygen delivery and not oxygen demand, but in the low dosage used in this study the changes were small.

On balance, it is unlikely that changes in sedation (even from Ramsay level 2–3 to 5) as in this study, significantly affect the oxygen demand/consumption balance. Extreme agitation and conversely cardiac depression should be avoided, and patients in whom oxygen delivery is markedly reduced should be mechanically ventilated if evidence of a tissue oxygen debt is apparent e.g. elevated lactate concentration or critically low SvO_2 .

In summary, controlled propofol sedation in the stated dosage is well tolerated in appropriately monitored and resuscitated patients, even when they require cardiovascular support with catecholamines. It is likely that there is no clinically significant effect on global oxygen transport.

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The subjective effects of low-dose propofol

A double-blind study to evaluate dimensions of sedation and consciousness with low-dose propofol

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Summary

In this study the subjective effects (sedation and mood) of subanaesthetic doses of propofol were examined in 28 healthy male volunteers. A computer model was used to predict the infusion profiles necessary to obtain steady state propofol plasma concentrations of $0.3 \mu\text{g.ml}^{-1}$, $0.6 \mu\text{g.ml}^{-1}$, $0.9 \mu\text{g.ml}^{-1}$. Objective measures of sedation from saccadic eye movement and choice reaction time gave significant dose responses at each level but a battery of psychometric tests failed to show dose-related subjective responses. Of particular note in the subjective data is the lack of a difference between groups or even of a consistent trend within the data. This suggests that a low concentration of propofol in plasma does not induce euphoria or a sense of well-being. The anecdotal evidence available for mood changes with propofol therefore remains unsubstantiated.

Key words

*Anaesthetics, intravenous; propofol.
Measurement techniques; psychometric tests.*

Sedation is frequently associated with altered states of consciousness and drowsiness. But the term *sedation* has been defined as 'a state in which pre-existing anxiety is removed or lessened or in which signs of anxiety do not develop in circumstances in which they would be expected to do so' [1]. Thus sedation need not be synonymous with altered consciousness.

Three dimensions of sedation have been suggested: consciousness, calmness and comprehension [2]. Whilst these may have an intuitive attractiveness, a better basis for further work would be established by the collection of data on the subjective aspects of sedation which could then be formed into a suitable set of working dimensions.

It has been shown that propofol provides suitable sedation as an adjunct to spinal blockade [3]. It has been compared with midazolam and shown to produce a more rapid recovery with less amnesia [4–7]. When used as an anaesthetic agent, recovery from propofol is much quicker than from other agents [8,9], with some benefits persisting up to 2 days following anaesthesia with propofol as the sole agent [10].

Over the past 3 years there have been several letters published in the medical journals describing unusual emer-

gences from propofol. For example, doctors from the Middlesex Hospital reported experiencing amorous advances from female patients [11]. This experience was echoed by other clinicians [12,13] and was not only limited to female patients [14]. Occasional more serious problems have also been reported; one woman experienced a very realistic postoperative hallucination of a sexual assault [15], whilst a male patient became very distraught by an unpleasant wartime dream [16]. However, it should be noted that in these cases propofol was not the only agent in use and there is no evidence that propofol was responsible, even as a facilitator. In a study of more than 300 male patients following anaesthesia induced with propofol, no erotic dreams were reported [17].

Apart from amorous and disinhibited behaviours it has also been noted, albeit anecdotally, that patients who are anaesthetised with propofol seem not only to recover rapidly, but often experience an increased sense of well-being [18] or a mild euphoric state [19]. A straw poll of our colleagues endorsed this. It is possible that this sense of well-being arises from a feeling of relief that the operation is over, an effect which may be dissipated in other patients who are feeling unwell in response to the anaesthetic. It has

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